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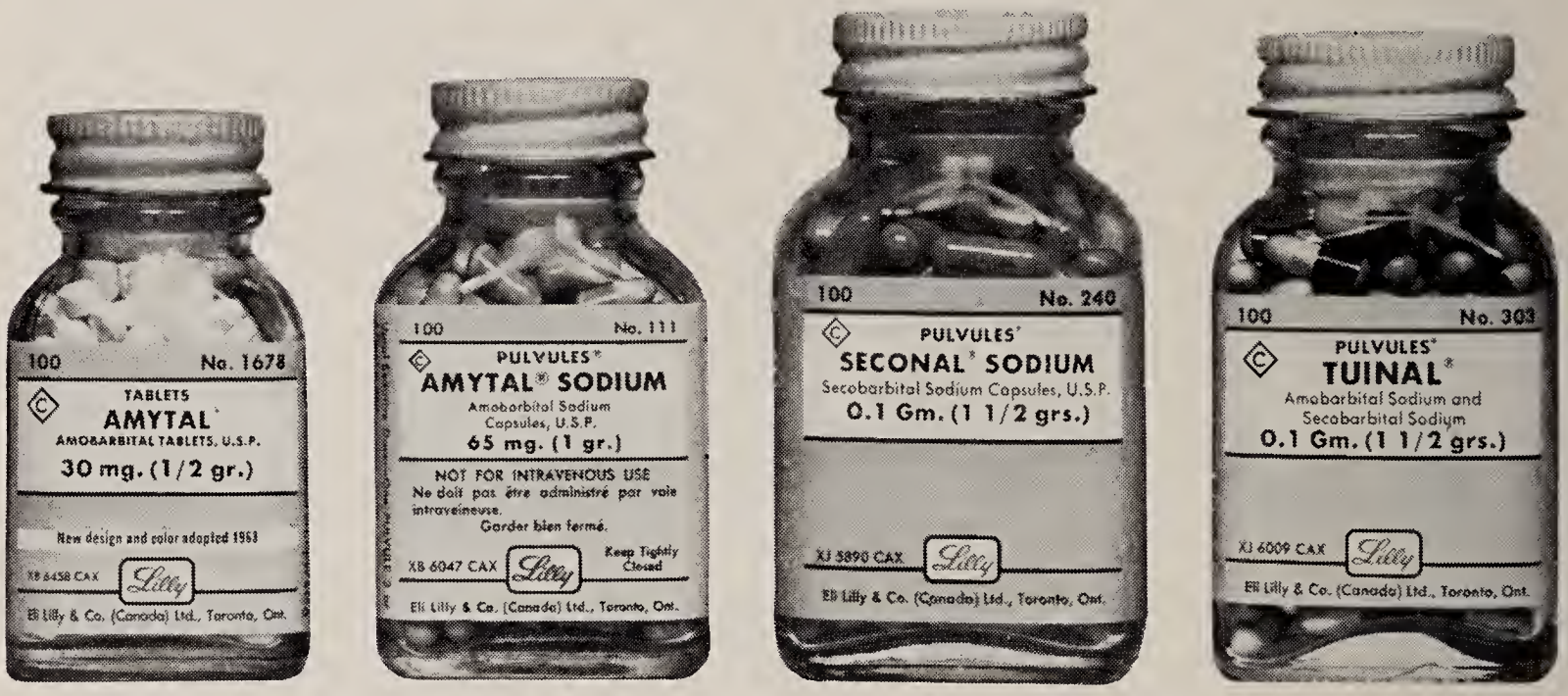

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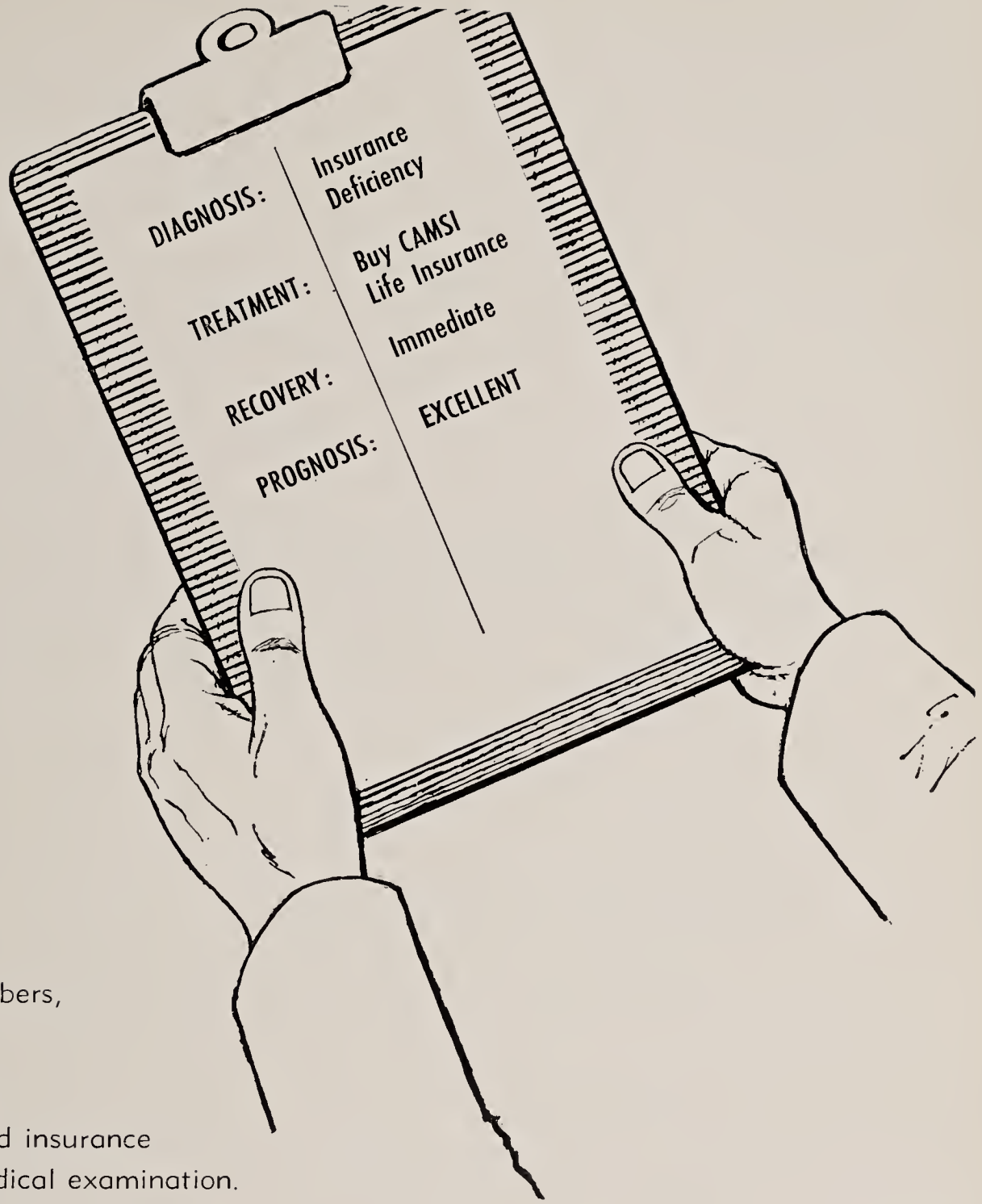

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Editorial

Neurology: Past, Present, Future

Neurology is the study of the nervous system whose normal function has been disturbed by disease or injury. To understand the aims of modern clinical neurology, it is necessary to trace its development from the beginning of the 19th century.

'Neurological medicine began as a clinicopathological discipline.' [1]

'Half a century ago a neurologist reached the apex of his proficiency near the end of a life of busy practice during which he had exhaustively examined many patients, among them those who were later to reach the post mortem table. Thus, in time, he became an accurate judge of localization and of the kind of lesion . . . his knowledge of the names, places, and connections of anatomy was superb; . . . his physiology was static, his chemistry nonexistent. . . . By contrast, his preoccupation with the details of pathology was intense. Morbid Anatomy was the core of his discipline.' [2]

These two authors pointed out the deficiencies in neurology training around the turn of this century. Too much emphasis was placed on the study of anatomy, pathology, and physiology. Clinical neurological investigation was limited to intense, minute dissection of symptoms and signs and their correlation to the forementioned basic sciences. Walshe[1] stated that, 'clinical neurology had become a precise and complex study of phenomena, primarily from the nosological, that is, from the classifying and descriptive, angle and for the identification of new disease states with their underlying pathology; and there was no general interest in the possible physiological import of the refinements of observation in which we indulged'.

Unfortunately, there is still today an undercurrent feeling that while some research in the field of neuroanatomy and neurophysiology is of value to the clinical neurologist, the fields of neurochemistry and biophysics are beyond the scope of a neurologist in training. Walshe[1] reported that 'so strong became this anatomical and physiological orientation of the clinical neurologists that the tradition was born that research into the anatomy and physiology of the nervous system was the most superior and important field of research for the neurologist. . . . it would be difficult to assess the vast resources of manpower, laboratory space, equipment, and expense that has gone into the electrophysiology of the clinician: electroencephalography and now electromyography, and how little, in proportion, into the study of those age-old burning problems of the etiology, pathogenesis, and treatment of the many chronic, disabling, and hilling affections of the nervous system'.

Although studies in the fields of anatomy, pathology, and physiology are of great import to the neurologist, they should not be given a 'number-one research priority.' Walshe[1] believes that 'it is time we gave ourselves more seriously to those modes and fields of research in which alone we can hope to find the solution of our urgent and unsolved problems, such as the fields of enzyme chemistry, of tissue culture, of biochemistry and physical chemistry, and the study of structure by the means the electron microscope has provided.'

The future of neurology depends on encouraging young neurologists becoming familiar with modern chemical and physical disciplines and using them to elucidate the heither to undiscovered etiology of many nervous diseases or their cure. 'Consider for a moment all those elucidations of the nature of some nervous affections, and the successful treatments of others that the past thirty years has seen: the treatment of the bacterial infections, the understanding and treatment of Vitamin B_{12} deficiencies and of other vitamin deficiencies. The elucidation and treatment of certain errors of metabolism affecting and damaging the nervous system; how much of all this has come from within the field of neurology? Am I not right in saying that we owe them all to workers outsire our field?

This is not the case in internal medicine today, and it need not be the case with neurological medicine any longer.

. . . I was born too soon to see from the Pisgah heights of modern chemistry and physics what fair perspectives of fruitful and healing research now lie spread before the younger generation if we who are older will but make it possible for them to enter this promised land.

. . . . However, I do not deviate from my view that the foundations of clinical neurology remain clinical investigation and morbid anatomy.' [1]

'Despite a formidable array of new equipment, the neurological sciences are sadly deficient in mature theory, such as might permit the full exploitation of our apportunities. Today, we continue to formulate our problems as did Hughlings Jackson, fifty years ago.

. . . a deficiency in the field of general theory must be made up.' [2]

The two authors believe that neurology has a great future. 'With the broadening of basic science training, including grounding in physics, chemistry, and mathematics, theorists should develop among us (neurologists) to correct this deficiency.'[2] Walshe[1] concludes 'in the new orientation and unifying of neurology a great future lies before it.'

A.G.L.

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Peripheral Neuropathies

PART I: *Michael A. Baker* 6T6

The peripheral neuropathies are best defined simply as those diseases that affect the peripheral nervous system, and as such can be considered a common neurological problem. No one classification of the peripheral neuropathies has proven satisfactory since there is still only scanty knowledge of their etiology and pathogenesis, therefore they are perhaps best divided etiologically into two groups, the "knowns" and the "unknowns".[1] The "known" group includes those neuropathies associated with toxins and deficiency states where it is felt that the etiology can be stated with some degree of certainty. The "unknowns" cover the vast majority of the peripheral neuropathies and until they can be transfered into the first group, are best classified according to their histological changes, that is into (1) parenchymal, if the nerve or its myelin sheath are affected, and (2) interstitial, if connective tissue or blood vessels are involved.

An understanding of the physiology and microscopic anatomy of the peripheral nervous system is essential to an understanding of the peripheral neuropathies and for these basic principles the reader is referred to the appropriate textbooks.[2,3] Suffice it here to say that an intact myelin sheath with its regularly spaced nodes of Ranvier is necessary for Saltatory conduction to occur. In this phenomenon the whole internodal distance is depolarized by the local circuit action which allows for more rapid conduction than seen in demyelinated fibres. Thus fragmentation or destruction of the myelin sheath structure will lead to decrease in conduction time even though the nerve axon itself is still intact.

Although no major breakthrough has occurred in our understanding of peripheral nerve disease, significant progress has been made towards elucidating the mechanisms operating in some of the common and less common neuropathies. It is the purpose of these papers to outline some of the more recent advances that have been made in this field. The first paper deals briefly with four peripheral neuropathies, namely metachromatic leukodystrophy, Refsum's syndrome, the peripheral entrapment neuropathies, and those associated with malignant disease. The third paper will look in depth into the work being done on the Guillian-Barre syndrome, and the second paper will discuss the recent insight being gained into the diabetic and alcoholic neuropathies.

METACHROMATIC LEUKODYSTROPHY

Metachromatic leukodystrophy is an uncommon affliction that has recently come into the limelight in neurology since it has been found to have an underlying biochemical disturbance contributing to its pathogenesis. It is a familial disease that usually appears in infants in the second year of life and ends fatally three to four years after onset,[4] however an adult form is also recognized that has similar clinical and pathological features.[4,5] The clinical abnormalities are largely due to central nervous system involvement since muscle wasting does not occur and the limbs become spastic rather than flaccid as the disease progresses. Tendon reflexes, however, are often depressed and "pins and needles" paresthesias have been reported, findings that strongly suggest peripheral nerve damage.[6]

The pathological changes[4] in the central nervous system consist of scattered areas of demyelination and occasional severe loss of axis cylinders with the pathognomonic sign being the presence of metachromatically staining lipid granules. Examination of the peripheral nerves[4,6] shows segmental demyelination with the metachromatic granules appearing the Schwann cells, but the nerve axons being unaffected. These findings suggest that the basic abnormality in the peripheral nerves might be some defect of Schwann cell metabolism leading to disintegration of myelin but leaving the axon structure unimpaired.[6] This has been supported by the fact that most of the abnormal nerve fibres were still capable of conducting nerve impulses despite marked slowing of conduction time.[6]

Recent biochemical investigation has shown that this disease stems from a disorder in the metabolism of sulphatide, one of the normal lipid constituents of myelin.[4,7,8] The sulphatides and cerebrosides comprise the glycolipids that are normally present in myelin, and there is now good evidence that brain, liver, and kidney contain an enzyme (cerebroside sulphatase) that normally removes sulphate from sulphatide to form cerebroside. In metachromatic leukodystrophy, there is a marked decrease in the activity of this enzyme,[7] so that the resulting buildup of sulphatides and decrease of cerebrosides leads to disruption of the delicate and intricate pattern of myelin formation that normally occurs at the infant's nervous system matures.[7] The fact that the myelin is a metabolic stable tissue after initial formation accounts for the observation that the disease is not commonly seen in adults, and that when it does appear, it follows a somewhat modified course.

The pathological and biochemical understanding of this disease has led to several useful laboratory aids to diagnosis. Microscopic examination of centrifuged ur-

ine using appropriate stains will show metachromatic granules, and chromatography of the urinary sediment will demonstrate a large sulphatide spot.[7] Peripheral nerve biopsies have proven effective, and may be easily obtained by sampling a cutaneous nerve such as the sural nerve, or by sampling the myenteric plexus of the bowel by rectal biopsy.[4 6] Motor nerve conduction studies have proven useful as a simply screening test in selecting cases for nerve biopsy.[6]

REFSUM'S SYNDROME

Refsum's syndrome[9 10 11 12] is a rare hereditary disease usually recognized in the second or third decade of life. It is characterized by (1) an atypical retinitis pigmentosa with concentric constriction of the visual fields, (2) a chronic polyneuritis with progressive paresis in the distal parts of the extremities, (3) an elevated cerebrospinal fluid protein, and (4) ataxia and other cerebellar signs. Other less common manifestations are anosmia, pupillary abnormalities, deafness, ichthyosis, alterations in the electro-cardiogram, and skeletal anomalies. The clinical course of the disease is variable and unpredictable in that it may be progressive in nature or stationary for long periods, or it may be characterized by remissions and exacerbations.

The pathological changes are similar to those of hypertrophic interstitial neuritis in that the peripheral nerves are swollen throughout their course.[11] All stages of myelin and axonal degeneration may be seen often in association wtih an endoneural fibrous tissue reaction that gives a characteristic onion-bulb appearance.[9 11]

Biochemical studies have revealed that Refsum's syndrome may also be due to a specific disturbance in lipid metabolism.[9] An abnormal branched chain fatty acid (3, 7, 11, 15-tetramethyl-hexadecanoic acid) never before described in humans, has been isolated from several patients with this syndrome. It is postulated that this acid is either an abnormal intermediary product or arises from a disorder of biosynthesis, and accumulates in organ fat to produce the clinical syndrome.[9]

PERIPHERAL ENTRAPMENT NEUROPATHIES

The peripheral entrapment neuropathies have stimulated recent interest since these syndromes are now found to be more common than previously suspected, and new sites of entrapment have been uncovered by studying the "stress anatomy" of suspected areas.[13 14] An entrapment neuropathy can be defined as a region of localized injury and inflammation in a peripheral nerve that is caused by some impinging anatomical structure.[13 15 16] A nerve may be trapped if it is fixed in relation to neighbouring structures such as osseus, fibrous, or osseofibrous tunnels, or such as occurs when a nerve changes course over a fibrous or muscular band. Examples of tunnel entrapment may be seen with the carpal tunnel syndrome involving the median nerve at the wrist or with the tarsal tunnel syndrome involving the posterior tibial nerve at the ankle.[15 16] The median nerve may also be trapped in the forearm where it passes between the two heads of the pronator teres muscle and then passes under the fibrous ligament of the flexor digitorum sublimus.[15]

Clinically, the common feature of the entrapment neuropathies is pain, that is usually present at rest and often most severe at night.[13 15 16] If a sensory nerve is involved, the pain tends to radiate over the distribution of that nerve and may be accompanied by hyperesthesia, hypesthesia, or paresthesia, but if the injury is primatily to a motor nerve, the pain tends to cover a wider region, with poor localization. Motor nerve involvement tends to cause a dull ache in the innervated joints as well as muscle tenderness, atrophy, and a variety of pains in the innervated muscles. The nerve trunk itself is frequently tender both distally and proximally to the site of involvement and pain may radiate along a nerve trunk for a considerable distance. Pressure over the suspected entrapment point should cause both local tenderness and aggravation of the proximal and distal symptoms.

There are two aids to diagnosis that have proven useful. The first is paraneural infiltration of the suspected region with an anti-inflammatory agent such as hydrocortisone.[13 15] This may actually effect a cure if there is only a minor degree of inflammation present, provided that the initiating traumatic factors are no longer operating. The injection is more likely to produce transient relief only, but it then serves to indicate that inflammation is playing some part in the etiology of the pain. The measurement of nerve conduction velocities has also led to fairly accurate pinpointing of the lesion since in many cases there is a slowing of conduction time past the point of involvement.[14]

The basic pathology at the site of entrapment seems to be an inflammation of the nerve itself, although cases have now been reported where lipomas or hematomas of the nerve,[17 18] or disease of the fibrous tunnels themselves[19] have been at fault. Inflammation of the nerve may be caused by an external force applied to the region or by sudden stress on the nerve during active exertion of the limb. More often than not there is no obvious explanation for the injury except that repetitious abnormal movements may cause a cumulative traumatic effect.[14 20]

The natural history of the entrapment neuropathies is unpredictable in that they may remain static for long periods of time or undergo spontaneous remissions and exacerbations. Occasionally the symptoms will have an acute onset, run a short course of weeks or months, and spontaneously disappear, never to return. The treatment therefore will depend on the individual case, but in general consists of a trial of anti-

inflammatory medication followed by surgical removal of fibrous constrictions where indicated.[13 20]

Currently about twenty entrapment syndromes are commonly recognized, ranging from entrapment of the plantar nerves in the ligaments of the foot, to entrapment of the long thoracic nerve in the scalenus medius muscle of the neck.[13 15 16] Entrapment syndromes are being recognized where herniated intervertebral discs, and hypertrophic arthritic spurs or autonomic disturbances have previously been implicated. Research is being conducted into other syndromes of questionable etiology such as Bell's palsy and tic douloureux, to see if these may also be explained on the basis of entrapment mechanisms.[13 21]

PERIPHERAL NEUROPATHY ASSOCIATED WITH MALIGNANCY

Several syndromes involving the central and peripheral nervous system have been recognized in patients with underlying carcinomas.[22] Clinically these carcinomatous neuropathies seem to bear little relationship to the course of the associated malignancy and may antedate the discovery of the tumour by several years.[23 24 25] The neurological manifestations may undergo temporary remissions or variations in severity quite unrelated to the size and growth rate of the tumour, and removal of the malignancy may have no effect. The clinical presentations vary with the particular syndromes but in general the peripheral carcinomatous neuropathies present a mixture of motor and sensory deficit,[24 25] with weakness and wasting of the proximal muscles of the lower limbs and decreased deep tendon reflexes,[24 26] as well as persistent paresthesias and pains in the limbs, and eventual loss of all sensory modalities.[23] The pathological changes accompanying motor symptoms include damage to the anterior horn cells, Wallerian degeneration of the peripheral nerves, and myopathy of the larger muscle fibres.[26 27] Those with sensory neuropathies have been found on autopsy to demonstrate degenerative changes in the dorsal root ganglia and peripheral nerves, and scattered inflammatory lesions in the brain and spinal cord, all of which are associated with lymphocytic infiltration.[25]

The incidence of the carcinomatous neuromyopathies was 3.5% in a recent study involving more than 1400 patients with all types of cancer.[26] Carcinomas of the lung and ovary yielded the highest frequency of associated neuromyopathy with incidences of 16% and 16.4%. Carcinomas of the breast and stomach yielded 4.4% and 9.0% respectively.[22] To consider the converse situation, 18.5% of 151 patients with neuromyopathies diagnosed by biopsy had some form of malignancy.[26] The incidence of malignancy in those patients over 50 was 34%, and in males over 50 the incidence was 60%. Approximately half of the carcinomatous neuromyopathies are associated with carcinoma of the lung[22] with the most common histological type being oat cell carcinoma.

It is generally agreed that the neuromyopathies constitute a true non-metastatic complication of malignancy and can be added to the growing list of such complications. Vascular, toxic, and metabolic factors have all been implicated in the etiology of these neuromyopathies,[23 24 28] but the most popular concepts presently, involve viral or immunological theories. The viral theories[24 25 28 29] stem from the observation that the site of the lesion and the course of the disease are similar to known viral diseases. The immunological concepts[24-26, 28-31] are based on the recent discovery of antibodies against the cytoplasm of central nervous tissue in patients with sensory carcinomatous neuropathy. Some attempt has been made to correlate the two theories[25, 29] by suggesting that the viruses may be carried by the tumour and may liberate or modify tissue antigens by attacking nervous tissue. Alternatively, virus modified tumour cells may be antigenic and share some determinants with the nervous system. These theories, however, are sheer conjecture and it remains for a virus to be isolated and for experimental immunological models to be set up. As with the other non metastatic complications of malignancy, it is hoped that research into the etiology of the carcinomatous neuromyopathies may shed some light on properties of malignant tissue that are presently unknown.

SUMMARY

This paper discusses four peripheral neuropathies that are of current interest in neurology: metachromatic leukodystrophy and Refsum's syndrome that are now known to be due to abnormalities of fat metabolism; the peripheral entrapment neuropathies that are being more frequently recognized as a cause of pain and muscle wasting; and the carcinomatous neuromyopathies that may lead to a better understanding of the nature of malignant tissue.

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PART II

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Single or multiple areas of peripheral nerve involvement, resulting in varying degrees of sensory and motor disturbances is a common finding among hospitalized patients. Chronic alcoholism, pregnancy, diabetes, amyloid and beri beri constitute but a few of the many metabolic or deficiency diseases associated with this syndrome. In some diseases the etiology and pathogenesis of the neuropathy are known while in others the arguments continue. One example of each type has been chosen for discussion in this article in an attempt to clarify the various theories and explanations put forth in the literature.

Of the metabolic causes of peripheral neuropathy, diabetes and alcohol are the most commonly encountered. In both cases there are varying degrees of symmetrical or asymmetrical sensory impairment with or without motor weakness which is most pronounced over the distal extremities. There are electromyographic changes common to both including decreased motor nerve conduction without loss of motor end plates in the affected limb.[1]

PHYSIOLOGY

A peripheral nerve is a biological complex of nerve cell, axon, Schwann cell and interstitial fluid. The axon consists of a tube of cytoplasm maintained primarily by the neuron. Experimental work has demonstrated that the Schwann cell may also contribute to the axonal maintenance peripherally, acting as a blood-nerve barrier.[2]

The nervous system depends almost entirely on carbohydrates as a source of energy[2] and it is therefore extremely susceptible to damage if its prime source of metabolism is compromised.

DIABETES

Introduction

Fifty per cent of all diabetics have some form of peripheral nerve imvolvement but in only 4% is the involvement symptomatic.[3]

Pathology

Patchy demyelinization, with no characteristic distribution of the remaining myelin sheaths is the most common finding. Some of the remaining sheaths contain only fat droplets and appear to be in the early stages of a slow but progressive demyelinization.[1] In most cases the axis cylinders remain intact even when the adjacent myelin is destroyed. Often the nutrient vessels to the nerve are surrounded by local collections of lymphocytes; and in some areas, scarring with total obliteration of nervous tissue is the prominent microscopic finding.[1,4]

As is seen clinically, distal segments are more severely affected than proximal ones and the lower limbs are more often involved than the upper limbs. In late stages, secondary changes in the cord and muscle are also seen.

Of interest is the fact that pathologic changes of neuropathy are more common in diabetic patients with renal and retinal pathology (mainly vascular) than in early diabetics, without vascular involvement.

Clinical

The pathological changes described manifest clinically in four ways.[5]

(i) *Radiculopathy:* This is due to nerve root involvement (usually posterior) with the resultant pain and loss of sensation confined to one dermatome.

(ii) *Mononeuropathy:* This syndrome is due to involvement of a mixed spinal or cranial (usually IV or VI) nerve with the clinical findings restricted to that nerve distribution.

(iii) *Polyneuropathy:* The glove and stocking distribution of the sensory and/or motor loss suggests a diffuse involvement of the peripheral nerve terminals.

(iv) *Autonomic system:* Involvement of this system, usually found in the elderly, frequently presents as nocturnal diarrhea, impotence, and urinary incontinence.

The most frequent form of clinical presentation is a bilateral distal neuropathy, predominantly sensory, in a glove and stocking distribution.[5] There is frequently a gradient of loss from affected to nonaffected areas with no sharp dividing line. Loss of sensation and/or associated cutaneous pain are most often the presenting symptoms while motor weakness is not prominent.

ETIOLOGY

1. Vascular Theory

One of the most serious complications of the diabetic state is the development of generalized vascular disease. Vascular sclerosis occurs both in the large vessels and in the vessels which supply the skin, retina, kidney and peripheral nerves.[4] It appears that poorly controlled diabetics are prone to develop both vascular and peripheral nerve changes. Keiding[6] has suggested that the patchy demyelinization and fibrosis found in the poorly controlled diabetic, is related to the atherosclerotic changes of the small nutrient vessels. Major peripheral nerves, especially the ulnar, radial and peroneal are subject to abrupt impairment suggestive of an acute vascular occlusion of the vasa vasorum. Histological study has shown the thrombosed vessels and the segment of infarcted nerve this is evidence that in some diabetics, vascular occlusion is an important element in neural dysfunction.

This theory does not however explain the findings of neural dysfunction in those cases seen without apparent underlying vascular pathology. Consequently newer theories, either based on or incorporating metabolic changes, have recently come into favour.

2. Metabolic Theories

a) Locke[5] has formulated that the neuropathy is due to a metabolic impairment with failure of axoplasmal formation before the distal terminals have been reached. He did not expand further on this metabolic impairment but did mention an additional finding—that of an elevated CSF protein. He thought this may have been due to a defect in the vascular permeability of the vessels.

b) Coors[7] did a study on 'latent neuropathy' among diabetics to determine the pathology and pathophysiology occurring at subclinical (asymptomatic) levels of the disease. His explanation for the lack of clinical findings in spite of underlying pathology was that at the same time that regressive pathological changes of demyelization are occurring, regenerative changes consisting of collateral ramifications of the motor axons are taking place. Simpson[2] postulated that the stimulus causing this regeneration is a chemotactic one originating from denervated muscle or sensory endings. In summary, the collateral ramifications of motor axons outpace the dystrophic alterations of the terminal arborizations. Thus, the patient rémains asymptomatic.

Coors' patient population[7] consisted of diabetics with sensory and/or motor nerve disturbances. One of his first observations was that in all patients, neural conduction velocity was decreased both in clinically affected *and* nonaffected regions of the same patient. He then studied the pathology of these clinically nonaffected nerves and found:

1) Terminal arborizations had shrunk and the teledendriacal expansions had become closely packed, eventually fusing into a single mass. These masses were, however, able to ensure satisfactory neuro-muscular transmission with no resulting clinical deficit.

2) The distal disintegration of axon cylinders was overshadowed by a collateral ramification of nerve fibres. In these patients decreased tendon reflexes were the only clinical findings.

Coors postulated[7] that the decrease in available insulin in the diabetic led to inefficient carbohydrate metabolism and subsequent 'malnutrition' of the dependent peripheral nerve leading to demyelinization. This theory does not explain the clinical phenomenon of peripheral neuropathy appearing *after* the onset of insulin therapy and subsequent metabolic control.[8]

To Coors the vascular theory of etiology was unacceptable on the grounds that a significant correlation was lacking between the presence of peripheral vascular change and the neuropathy. He felt that the vascular theory was also unable to explain the paucity of similar symptoms in an arteriosclerotic hypertensive patient. One must remember however, that in the diabetic there is a far greater small vessel involvement (not seen in the hypertensive) which might explain this discrepancy.

c) Hoffman[9] studied neuropathy among the young and elderly diabetic and drew the following conclusions: 1) In younger diabetics the neuropathy is mainly a metabolic deficiency — one of avitaminosis associated with nutritional derangements and faulty carbohydrate metabolism. In most cases the neuropathy can be reversed with adequate control of the diabetes. The presenting symptomatology of nocturnal leg pain is usually cleared up at the same time.

2) Among the older diabetics painless neuropathy may develop leading to Charcot joints. Autonomic nervous system dysfunction such as nocturnal diarrhea, urinary

incontinence, impotence, and postural hypotension is a prominent finding which is not always reversed with good diabetic control. In view of the widespread atherosclerosis commonly seen in this group, Hoffman postulated that both vascular and metabolic dysfunction play important roles. He felt that in either case vascular disorders alone were unable to explain the neuropathy since:

i) Although arteriosclerotic phenomena are observed in the neuronal vasa vasorum of the elderly diabetic, there are sufficient unaffected blood vessels to provide adequate blood supply. In view of the rich anastamotic blood supply, it would take massive vascular involvement to produce this clinical picture.

ii) Neuropathy is seen in prediabetic states with no evidence of arteriosclerosis.

iii) Arteriosclerosis is relatively irreversible but diabetic neuropathy is frequently reversible, especially among the younger. He noticed that improvement occurs if a diet high in Vitamin B1 is given and therefore thought that avitaminosis plays an important part in the neuropathy. This view is not held by most writers on this subject, and there is no good evidence that avitaminosis plays a role in the development of neuropathy.

There are theories which postulate a build-up of metabolites in poorly controlled diabetics leading to the neuropathy. These theories do not explain why neuropathy is less frequently seen among children, who are more prone to acidosis and ketosis than among the more stable adults.

To further confuse the issue Martin has shown that the poly-neuropathy is unrelated to blood sugar levels and that some diabetics develop the neuropathy after the onset of insulin therapy.

Treatment

To date a reasonable program of treatment would consist of:

1. Rigid control of the diabetes.[7 8 9]

2. Bed rest with physiotherapy.[7 8 9]
(Bed rest is of greatest value in the early stages of the disorder).

Summary

The theories of metabolic dysfunction propose a depleted supply of metabolites to the peripheral nerves due to impaired glucose metabolism. In the younger diabetics these theories appear sufficient but in the older diabetics the vascular insufficiency secondary to atherosclerosis must also be considered, especially in cases of acute mononeuritis.

Many questions remain unanswered:

i) What is the role of insulin therapy in precipitating the onset of neuropathy?

ii) What is the relation between good diabetic control and recovery from neuropathy?

iii) What is the basic metabolic defect that renders diabetic patients prone to neuropathy?

ALCOHOL

The findings of hepatomegaly, spider naevi, and peripheral neuropathy constitute one of the commonest syndromes seen by the student on the public wards of the teaching hospitals. As more striking neurological findings are also usually present, the findings of neuropathy are occasionally put aside and often ignored — especially if the patient is asymptomatic.

Pathology

The most common findings are those of degeneration of the peripheral nerves with subsequent involvement of the anterior and posterior nerve roots.[1 4] The myelin is destroyed initially and to a greater extent than the axons, with the process beginning distally and progressing proximally.

In some areas short segments of myelin degeneration with intact axons are found, while in others Wallerian degeneration[4] is the rule. This degeneration consists of:

i) A shrinking and distortion of the cylinders.

ii) A breaking up of the axis cylinders and myelin.

iii) An infiltration by histiocytes and macrophages.

iv) Proliferation of Schwann cells.

v) An eventual regeneration of the axis cylinders.

Pathochemistry

The alcoholic diet consists primarily of alcohol (carbohydrate) with little or no protein, vitamin, or mineral supplementation. With deficient thiamine intake:

i) Anorexia develops which further reduces the amount of nonalcoholic food ingested.

ii) The body stores of thiamine are depleted.[10]

Thiamine is required for the normal oxidative metabolism of pyruvic acid in the cycles involving glucose metabolism.[10 11] With thiamine deficiency, pyruvate accumulates in the tissue fluids and blood, while the axon and myelin are deprived of their only source of energy.[12]

Clinical

It has been well documented that no essential clinical or pathological difference exists between the neuropathy of beri and that of alcohol.[8] Presenting complaints are diverse and patients are often asymptomatic with respect to neuropathy; this neuropathy is often first

noticed on routine physical examination. The findings among asymptomatic patients are:[7]

i) A slight decrease in the size of the leg muscles.

ii) A slight but unnoticed loss of power in the legs.

iii) Decreased deep tendon reflexes in the lower limbs.

iv) Deep calf tenderness to pressure, with impaired superficial pain and temperature sensation.

Among the symptomatic patients the onset of neuropathy is usually insidious with slow progression of signs and symptoms. Occasionally, there is a sudden onset leading to paralysis. Complaints are initially referred to the lower limbs with the greatest affliction in the distal portions.

Although some weakness may be present in the lower limbs it is not usually severe enough to be incapacitating. Physical findings are symmetrical and concentrated distally. Even with the mildest degree of leg weakness, the patellar reflexes may be absent. In the upper limbs the reflexes (C 5, 6) may be retained in spite of gross peripheral muscular weakness (involving muscles innervated by C 7, C 8, T 1). Occasionally, in patients with severe parasthesiae, the deep tendon reflexes may be brisk. The point to remember is that peripheral nerves may be involved despite the findings of normal or hyperactive tendon reflexes. Wernicke's syndrome includes a special type of neuropathy involving the occulomotor nerves.[13]

Pain was the most distressing complaint among those who developed nutritional neuropathy in prisoner of war camps[14]. However, among alcoholics, pain is not the primary complaint. It is the numbness, prickling, deadness and coldness, occasionally associated with a deep calf ache which brings the alcoholic to the physician.[15] Often, the sensory disturbances are so great and so distressing that the patient is unable to walk in spite of normal motor function.

All modalities of sensation are usually affected, but often, one modality is affected to a greater degree. There is no sharp demarcation between normal and hypoasthetic areas, but rather, a gradual zone of transition.[16 8] Because of the parasthesiae and the exaggerated sensations experienced during the delirium tremens, alcoholics with neuropathy are occasionally labelled 'hyperasthetic'. This is a misnomer and should be avoided, since there is an underlying elevated threshold to various stimuli. However, once a stimulus is perceived, it may take on a very unpleasant quality.

Etiology

a) Spillane[17] has suggested a nutritional imbalance affecting the peripheral nerves of the extremities, with the same end results seen with vascular insufficiency i.e. a decrease in available nutrients.

b) Jumbo,[15] studied motor nerve conduction in alcoholics with neither signs nor symptoms of peripheral neuropathy. Compared to normal controls, the alcoholic population show a significantly depressed motor nerve conduction velocity. Within the alcoholic group, there is no significant difference between the conduction of nerve impulses in the asymptomatic or in the mildly symptomatic. Furthermore there may be no difference in conduction in the alcoholic who has suffered from D.T.'s and the milder alcoholic. These results suggest:

i) Damage to peripheral nerves occurs earlier than expected in alcoholics.

ii) Damage may occur before clinical signs of neuropathy occur and before E.E.G. changes indicate any central nervous system involvement.

c) Finnley[16] reported that the neuropathy is a result of malnutrition involving the B complex vitamins, thiamine and pyridoxine. Pyridoxine is important because it forms part of the coenzyme necessary for transamination and specific amino acid oxidation, and is necessary for the conversion of tryptophane to niacin—all essential for glucose metabolism. His laboratory findings were:

i) Blood thiamine levels are significantly depressed in 47% of alcoholics without neuropathy and 86% of alcoholics with neuropathy.

ii) Blood folic acid levels are depressed in the majority of alcoholics.

iii) In 90% of alcoholics with neuropathy a combined vitamin B deficiency is demonstrated.

In alcoholics with a diet deficient in protein, hepatic disease and neuropathy are likely to appear. The lowest levels of thiamine are found in patients whose diets consist mainly of alcoholic beverages.[14 10] Two theories[10 16] have been posulated to explain these findings.

1. The vitamin deficiency due to failure of intake may be aggravated by the failure of the liver to convert any free vitamin available in the diet into an active coenzyme.

2. Tho protein content of the enzyme systems is affected because of hepatic insufficiency. (Due to hepatic insufficiency, there is a decreased amount of protein synthesis resulting in impaired enzyme formation.)

It is therefore apparent that simple vitamin supplementation in the presence of a diseased liver inadequate therapy. Associated metabolic defects must be corrected at the same time to achieve adequate results.

If hepatic involvement is mild, marked clinical improvement occurs within 7 to 10 days of onset of vitamin replacement. In cases where a history of poor protein intake is obtained and/or signs of hepatic

damage are evident, a minimum of 6 months intensive therapy is required before adequate clinical improvement can be demonstrated.[15 16]

Treatment

1. Complete bed rest in the acute stages.[8 15 16]
2. Thiamine supplement in the diet-100 mg. per day.[8 15 16] (Normal daily requirements are only 1 mg.)[17]
3. Dietary supplements of minerals, proteins, and B complex vitamins.[15 16]

Summary

The proof of thiamine deficiency leading to decreased glucose metabolism and subsequently impaired 'neuronal nutrition' is well documented. Vitamin replacement alone, in the presence of hepatic damage and protein disturbance, is insufficient.

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The Landry—Guillain—Barré—Strohl syndrome is the eponym for what has been, and is known as: acute peripheral neuritis, acute infective neuritis, acute idiopathic polyneuritis, polyradiculoneuropathy, infectious neuronitis, et caetera, et caetera. This plethora of names is merely a reflection of both our ignorance of the aetiology and a confusion in the literature as to what the syndrome is, both clinically and in the laboratory.

HISTORY

Landry[1] in 1859 described ten cases of what he called acute ascending paralysis — 'ascending' being synonomous with the word 'centripetal' here. Generally, the features he described included: an onset usually after convalescence from an acute illness, a generalized weakness rapidly spreading distally to proximally often involving trunk and cranial nerves, a tendency toward more severe involvement of proximal muscle groups, and lower rather than upper limbs. He also noted the presence of varying degrees of sensory involvement, usually mild, which frequently affected acral touch and posture, often in a glove and stocking distribution. Paresthesias, as well as muscle pain and tenderness were also seen. Tendon reflexes were lost. Two patients died in respiratory failure but subsequent autopsy was unrevealing. Those who recovered, did so in a reversal of the onset pattern. One should note that Landry did not report on the cerebrospinal fluid of his cases, as lumbar puncture was not clinically introduced until some thirty years later.

In the next fifty years many clinicians described similar disease patterns covering all ages and races. During the years of World War I, investigators[2 3], both American and British, felt an infectious agent was responsible for the entity, thus names such as acute infectious polyneuritis and acute infective neuronitis arose.

Guillain, Barré and Strohl,[4] in 1916, described two patients with what is felt to be essentially the same disease as that described by Landry. These authors also noted a high albumin content plus a normal cell count present in the cerebrospinal fluid.

Since that time many clinical variations of this syndrome have been reported, as well as a multitude of arguments as to its etiology, definition and prognosis. One tends to agree with Munsat and Bornes[5] who feel that the syndrome should be considered in all of its ramifications, the only diagnostic criteria being (applied is that) those resting on a knowledgeable foundation.

As far as nomenclature is concerned, the eponym Guillain-Barré probably serves well, despite its historical omissions. The term acute idiopathic polyradiculoneuropathy however describes the course, etiology and pathology concisely and hence is growing in favour.

Now let us examine the nature and status of this syndrome as it stands today.

INCIDENCE

All races and age groups are susceptible, both generally following the population pattern.[8] As in many other diseases however, males are more prone than females—in this case in a ratio of 3:2 or even 2:1[6 7].

No clear seasonal variation has appeared in the literature save for a slightly increased incidence in winter and spring[7 8 9]. The prevalence of the disease in the population seems to be rising.[6] During the last five years at the Toronto General Hospital Respiratory Unit there were 23 cases of the neuropathy and only 7 cases of poliomyelitis.[10]

Thirty to eighty percent of cases are preceded by a febrile illness, the most common offenders being a mild upper respiratory or gastrointestinal infection. However, precursors such as infectious mononucleosis, the exanthemata, primary atypical pneumonia, infectious hepatitis and so forth are well known.[7 11] Seven cases have been reported in association with pregnancy, neither state having an effect on the course of the other.[12] There are also widespread reports of onset of the syndrome following serum injection, such as inoculation of antitoxin.[13 14] One case has been reported following the use of PAS in tuberculosis therapy.[15] Several patients, in a series presented by Humphrey,[10] developed their illness following surgery or trauma.

ETIOLOGY

The etiology of this disease is portrayed vividly by the word 'idiopathic'. Much research and speculation has been done, however, along the lines of infectious and allergic hypotheses.

Infectious

Guillain[16], as well as many others, feels that the disease is viral in origin. In fact, in the early part of this century, some investigators[2] published a report claiming to have transmitted the disease by spinal cord inoculation of primates. At present, however, this work has not been reproduced.

In 1949, two researchers[17] injected cerebrospinal fluid from a boy with acute polyradiculoneuropathy into the brains of mice, producing a disease characterized by palsies. An organism was cultured but not identified.

One interesting report[18] associates the disease with feline enteritis as the author observed several apparently connected cases. In one instance, a patient, ill with the syndrome sent his cat to a women for care. Remarkably enough, while feline enteritis killed the cat, the woman contracted the polyneuropathy and died.

Cerebrospinal fluid virus isolation from cases of the syndrome, usually of the ECHO[19 20] and Coxsackie[21 22] variety, have appeared sporadically in recent literature. Melnick[22] studied 52 cases, employing modern virological and serological techniques, in an attempt to uncover an offending virus. Coxsackie B5 was isolated in only two instances—both at a time when this virus was prevalent in the population of the area. None of his patients gave a history of contact with a sick pet, particularly cats. Though his results failed to support the infectious theory, the investigation did strengthen the impression that the syndrome tends to follow soon after a virus infection as positive histories were obtained in seventy percent of his cases. It was also noted that serologically proven subclinical viral infections of various types were found concomitantly in forty-eight percent of his patients.

The present concept, held by those who support a viral etiology, resembles that given for Herpes Zoster.[23] In short, a neurotropic virus or its toxin affects the nerve directly; this virus is so low in virulence, however, that the damage may be only minimal and hence the nerve may improve and eventually, may regain its original function.

Immune

Despite the tendency to overuse auto-immunity or allergy as an etiological factor in modern medicine, one cannot help but be impressed by the wealth of data implicating the immune mechanism.

Suspicion may be first aroused by the fact that acute idiopathic polyradiculoneuropathy is often preceded by febrile illness, serum injection, or even drug therapy. The onset of the neuropathy usually follows a latent period suggesting some degree of similarity to post-infectious encephalomyelitis and hence a neuroallergic phenomenon rather than a direct infectious attack on the nervous system.[11] Another explanation is akin to that proposed for the relationship of B-hemolytic streptococcal infection and rheumatic fever or acute glomerulonephritis. This latter theory is opposed by Melnick[22] on two counts. Firstly, he reiterates the fact that, unlike the streptococcal infection in these possibly cross-reacting or haptogenic disorders, both the nature and the subsequent latent period of the diseases preceding the syndrome are quite variable. Secondly, he studied the occurrence of auto-immune-complement-fixing tissue antibodies in association with the many virus infections encountered in his study on the infectious etiology of this disorder. None of the viruses, save mumps, showed a positive correlation.

Whitebsky[24] and his co-workers, in 1957, formulated four criteria which they feel must be satisfied before the label auto-immune could be attached to a condition. These criteria provide a basis with which to assess investigations proceeding along this line. They are as follows:

"(1) Direct demonstration of free circulating antibodies which are active at body temperature, or of cell-bound antibodies by indirect means.

(2) Recognition of the specific antigen against which the antibody is directed.

(3) Production of antibodies against the same antigen in experimental animals.

(4) Appearance of pathological changes in corresponding tissues of an actively sensitized animal that are basically similar to those in the human disease."

Criteria (3) and (4) were satisfied two years previously by Waksman and Adams,[25] who found that injection of rodents with homologous or heterologous nervous tissue and Freund's adjuvant produced a disease which, save for minor species differences, resembled acute idiopathic polyradiculoneuropathy both neurologically and pathologically. The distribution of their lesions depended on the neuro-antigenic preparation. They put forth the hypothesis that this latter phenomenon was due to immunological differences between the central and peripheral nervous systems. This hypothesis was verified two years later by Finean and his co-workers[26] who demonstrated structural and chemical differences between central and peripheral myelin. Their production of an experimental allergic neuritis has been substantiated on numerous occasions.

Further papers by Waksman and his co-investigators fulfilled the first criterion. They reported the finding of circulating antibodies, the concentration of which had no relation to the severity of the allergic disorder.[27] They also demonstrated that the disease could be passively transferred by means circulating mononuclear cells.[28]

A step towards satisfying criterion (2) was taken by Melnick[29] in 1963 who found that 19 of his 38 cases of acute idiopathic polyradiculoneuropathy had complement-fixing antibodies to normal human nervous tissue, some showing significant levels within a day of onset. High levels of these antibodies were found in patients with various hypersensitivity diseases as well as several chronic neuropathies. One-quarter of his Guillain-Barré patients, in which the cerebrospinal fluid was investigated, showed these antibodies in the fluid. One case out of the four assessed thusly, with chronic peripheral neuropathy, was also positive—other neurological patients had a rate in the order of 3%. The incidence and titre of other auto-antibodies was found to be lower in the Guillain-Barré syndrome than in the so-called auto-immune diseases.

At present, criterion (2) remains as a stumbling-block to the establishment of an auto-immune etiology for, in spite of intense investigation, "the specific antigen against which the antibody is directed" has not been identified.

PATHOLOGY

The most extensive and authoritative pathological description to date is the treatise of Haymaker and Kernohan.[8]

These authors studied the pathogenesis in a series of fifty fatal cases—death varying from 2 to 46 days after onset. Unfortunately, these authors did not have sufficient peripheral nerve material to investigate adequately. However, subsequent study, in addition to substantiating their findings, has demonstrated similar changes in peripheral nerves[30]—variable degrees of segmental and Wallerian degeneration being most prominent. The pathological findings correspond closely to the neurological involvement both in distribution and in nerve components affected. Nerves, ganglia, and roots are primarily involved but the central nervous system may also show pathology.

The first feature to be visualized is oedema, usually in evidence by day 2 or 3. Axonal and myelin degeneration soon follow. By day 9, scattered groups of lymphocytes appear on the scene in increasing numbers and eventually, phagocytes join the infiltration. In under two weeks, Schwann cell proliferation may be noted. Cases which are fatal after a prolonged course may show marked degenerative changes in the spinal roots, peripheral nerves and even the dorsal columns. The meninges are usually spared, while central nervous system findings generally appear to be either secondary, or of the nature of perivascular collections of lymphocytes with or without gliosis. Cerebral oedema has been demonstrated.[32]

Richter, in 1962[33], noted that the ataxic form of the polyradiculoneuropathy may resemble tabes dorsalis not only clinically but sometimes pathologically. Neurological degeneration in the middle root zone of the posterior columns and columns of Clarke were predominant features of his one fatal case.

Pathological changes, eleswhere in the body, are variable and include interstitial myocarditis, focal hepatic necrosis and infiltrative and/or mild degenerative changes in muscle as well as foci of inflammatory cells in other organs.[8 30 31]

Electron microscopy[34], indicates that the myelin degeneration is apparently a physical fragmentation rather than a chemical disorganization. The authors, Finean and Wolfe, have postulated that the unknown agent responsible for the pathological picture causes a primary degeneration, and hence shrinkage, of the axis cylinder. This, in turn, leads to a physical disruption of the orderly spiral layering of the myelin sheath, resulting in fragmentation of the myelin.

The pathological changes in the affected nervous tissues shows a striking resemblance to those of experimental allergic neuritis, as has been stated previously, and thus is more in keeping with an immune etiology.[31]

CLINICAL PICTURE

Signs and Symptoms

In a disorder such as the Guillain-Barré syndrome, in which the clinical picture is so variable in terms of of onset, distribution, severity, and relative degrees of sensory or motor involvement, categorization of the manifestations into subsyndromes merely proves both confusing and incomplete. Furthermore, in any description of the disease, one should be aware of the impassioned argument in the literature as to what are the ramifications of the syndrome.

The general course[35 36] is that originally described by Landry[1], or Guillain, Barré and Strohl[4]. An infection, followed by a latent period, and then premonitory symptoms such as malaise, nausea, diarrhea, fatigue and general aches and pains usher in the illness. Fever is usually absent. A symmetrical, centripetal motor involvement of the limbs and/or cranial nerve musculature, notably the facial, soon follow and may progress to involve the trunk and diaphragm. Motor symptomatology is quite variable, and often includes ophthalmoplegia, dysarthria, dysphonia and dysphagia. Proximal muscle groups may or may not be more involved than distal ones. Lower limbs are usually more affected than upper limbs. Tendon reflexes are lost. Sensory findings include muscle tenderness and pain, paresthesias and loss of touch and posture—the latter in a glove and stocking distribution. Ataxia and, infrequently, papilloedema may be present. The entire body may be involved or the disease may be localized, appearing as a Bell's palsy or sciatica[37 38]. One must make sure that any evident mononeuritis is not what some authors call a pseudomononeuritis, in which much less overt neuritic manifestations elsewhere have been overlooked.

Although in most cases motor manifestations dominate the clinical picture, they may be overwhelmed by sensory ones—some authors[39] feeling that certain cases of pure sensory neuritis must be considered as a clinical form of the Guillain-Barré syndrome. Two interesting patterns of sensory involvement should be noted: one is descriptively called a symmetrical ascending polyneuritis, in which only the posterior roots are involved, in ascending order, clinically manifesting as a numbness which creeps upward from the feet—usually stopping in the thoraco—abdominal region; the other is a migratory sensory neuritis which is a wandering sensory disturbance affecting areas which are not necessarily neurologically contiguous. Many clinicians feel that the above forms are highly questionable variants of the syndrome.

Autonomic disturbances are found in the Guillain-Barré syndrome, with as many as 40% of cases showing some disturbance in sphincter control resulting in retention or incontinence, sometime during the disease course. Abdominal weakness may aggravate this problem. Circulatory abnormalities,[40 41] occasionally induced by inadequate ventilation, may also be associated with the syndrome and include hypotension, hypertension, a very labile blood pressure or cardiac arrhythmias. The latter two are ominous prognostic signs.[6]

Course and Prognosis

The disease usually consists of an acute onset, followed by progression of symptoms for one to three weeks, then a clinical plateau for another one to three weeks and finally, gradual recovery over a few weeks to years—most patients recovering within six months to one year. Relapses may occur. In the end, the patient may recover completely, or be left with some neurological deficit, the latter occuring in 5 to 15 percent of cases. About 10 to 40 percent of cases end in death. Hypoxia, the major terminal factor, may be due to respiratory paralysis, bronchopneumonia, aspiration or mucous obstruction of the airways. Myocarditis, resulting in cardiac failure or circulatory collapse, may also lend to the patient's demise.

Laboratory

Save for cerebrospinal fluid examination, laboratory findings are essentially unremarkable, unless the case is complicated by an accompanying condition. An infrequent but interesting exception, first noted by Haymaker,[8] is the appearance of foamy lymphocytes in the serum of patients with the syndrome. Although infectious mononucleosis is a well-known concomitant of the disease, many of these cases fail to show any of its other clinical or laboratory characteristics.

Opening pressure of the lumbar tap may be high in up to 20% of cases of the syndrome.[6] The cell count in the spinal fluid is usually normal[6]; pleocytosis when present, very rarely exceeds 50 cells per cubic millimeter unless a complicating feature is present. Most authors[6 7] agree that the spinal fluid protein will be above normal, at some occasion, in almost all cases—the most likely time being during week two or just after the illness peak. The literature records protein levels as high as 2000 mgm. percent[42 43], although levels are generally about 10 to 30 percent[7] of this value. Some authors have reported normal values, but it is generally felt that their punctures were done at the wrong time and not repeated subsequently.[7] The spinal fluid protein concentration shows no correlation to the clniical course and may remain elevated, or even increase during part of the recovery phase.[7]

As albuminocytologic dissociation may be found in several diverse conditions[39] such as diphtheric polyneuritis, TB meningitis, tumour and poliomyelitis, it certainly cannot be considered pathognomic of the Guillain-Barré syndrome.

One interesting feature that has appeared sporadically in the literature is the finding that the increase in protein in the lumbar subarachnoid space is out of proportion to that seen in the fluid taken from the cisterns—

a case being reported where the protein levels were as divergent as 2000 and 25 mgm percent respectively.[7 42]

At present, theories for the albuminocytologic dissociation are varied. The most widely held hypothesis[44 45] is that the oedema and vascular congestion of the nerve roots result in both increased vascular permeability (hence excessive protein leakage) and obstruction of cerebrospinal fluid outflow (hence diminished protein reabsorption)—both factors leading to a build-up in protein levels. Another hypothesis, posed by Poser and Curtis[46] is based on the argument that the above theory does not explain high levels persisting during the recovery phase. They then point out that the Schwannoma is the neurological neoplasm most often associated with high spinal fluid protein regardless of its location and whether or not spinal block occurs. Therefore, since the pathology of the Guillain-Barré syndrome has shown Schwann cell proliferation even during the recovery phase, and since the electron microscope has shown Schwann cells to be very metabolically active, they feel that conceivably the hyperalbuminosis in the syndrome "results from heightened activity of the greatly increased Schwann cells during the second phase of the disease".

The mechanism of the production of the papilloedema occasionally seen in the syndrome is cerebral oedema[22] in some cases, blockage of the arachnoid villi by excessive protein[44 45 46] in others, and finally unknown factors.

Other spinal fluid findings as well as electroencaphalographic changes are extremely variable and thus of no help clinically. Studies now being pursued, notably by Humphrey[10 47] and McDonald[48], show a varying degree of reduction of conduction velocity in the affected nerves. Impairment is most marked during the plateau period of the disease while recovery tends to parallel clinical return of function. There is some evidence that similar changes occur in experimental allergic neuritis.[49] The details are complex and will not be expanded upon here.

DIAGNOSIS

The diagnosis of the Guillain-Barré syndrome must be made by exclusion. At times this may be difficult, taking weeks of observation. Disorders to be considered include acute mono and polyneuropathies of known cause, poliomyelitis, polyarteritis, dermatomyositis, acute porphyria, myasthenia gravis, acute tetraplegia, tick paralysis, and hysteria. On the other hand, cases may be missed if, in the search for an etiological factor, an insignificant feature such as transient contact with lead or a very minor spinal osteoarthritis is overstressed and hence labelled as the cause of the neurological problem.

TREATMENT

General

Landry[1] originally treated his patients with a combination of massage, electrical stimulation, chops and Bordeaux wine. Although we have dropped the chops and Bordeaux wine, supportive therapy still remains in the forefront of the treatment programme of acute idiopathic polyradiculoneuropathy[6 50]. Early and adequate management of respiratory insufficiency, pharyngeal paralysis, or vascular collapse is mandatory. As onset of these complications may be rapid, watchful surveillance, and ready accessibility of necessary drugs, respirator and tracheostomy facilities are required. As in many other neurological disorders, proper physiotherapy and positioning, as well as skin, bladder and bowel care, are important ingredients of the therapeutic programme. Humphrey[10], in a review of 70 cases treated in the Toronto General Hospital, feels that pressure on the involved nerves tends to have an adverse effect on the clinical course and hence emphasizes the importance of positioning and proper padding of immobile limbs. One must also remember that experiencing this potentially widespread paralytic disease may be terrifying to the patient. Hence constant reassurance as well as psychotherapy, if needed, is advisable.

Specific

Specific treatment is still in a clinical-experimental stage. Over the last decade many cases have been treated with steroids or ACTH. Recently Heller and Dejong[51] reviewed over one-hundred published cases in which these drugs were used. Although they felt that both the disease course and prognosis were affected favorably, (recovery seemed to be accelerated and more complete with deaths taking a toll of only slightly over 6%), they admitted that a lack of both a truly controlled study and a large series, in such an unpredictable disease, left a 'post hoc ergo propter hoc'* rationalization of therapy a distinct possibility.[52]

Steroids[53] have been found to be of value in experimental allergic neuritis only if administered prior to the inoculation of antigen.

As convincing evidence regarding the value of steroids has yet to be presented, the concensus viewpoint would seem to be that in prolonged, rapidly progressive, or severe disease, steroid trial is worthy of consideration, providing no contraindications exist. The incidence of complicating infections, notably pulmonary, is high in these cases.

Recently a paper[54] has been published claiming rather striking results with the immunosuppressive and cytotoxic drug, 6 mercapto-purine. The drug appeared to

* 'after this, therefore because of this'

have an unmistakably beneficial effect on the course of the illness. However, the disease picture was atypical and hence a moot case of the syndrome. Undoubtedly this paper is a forerunner of a host of investigations along this line.

CONCLUSION

It is evident that the Landry-Guillain-Barré-Strohl syndrome is a multifaceted and interesting complex of symptoms and signs. At present, some authors feel that the diagnostic criteria are exact and rigid, while others feel that the syndrome is but a post-infectious polyradiculoneuropathy lying at an opposite pole to post-infectious encephalomyelitis, in a continuous spectrum of conditions in which the nervous system is the site of an immunological reaction following a virus infection. Most feel at present that although its definition may be vague and one of the exclusion, it certainly remains a distinct, valid and recognizable clinical syndrome. The wealth of research into this disorder is rapidly pushing the frontier forward. At present, its etiology seems to be almost surely immunological. Certainly, the raising of the veil of vagueness and mystery is imminent.

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Epilepsy Of Late Onset

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Convulsions present a diagnostic problem. They infer some profound physiological disturbance of cerebral function. Convulsions may be induced in any person by certain chemical agents, may be an expression of some systemic disorder like hypoglycemia, uremia, etc., or may be primarily a symptom of cerebral dysfunction manifesting itself as a 'recurring discrete disorder of sensation or behaviour of any sort.' [26] Williams[26] believes that only the latter condition may be considered as epilepsy although all three types of seizure patterns will be, from a scientific standpoint, the same. He feels that the term epilepsy implies an individual susceptibility to seizure discharges, not found in a normal person and thus making the diagnosis relative. However, before such a distinction can be made, systemic or extracerebral causes of seizures must be ruled out. It must be emphasized that epilepsy is a symptom like dyspnea and must never be considered as a disease enttiy but rather a manifestation (thereof).

TERMINOLOGY

The terminology used to subdivide epilepsy into general broad categories may be confusing and thus requires explanation. *Genetic, essential or centrencephalic epilepsy* are terms used to describe those seizures which usually, but not necessarily arise without warning (either grand mal or petit mal in type) and the E.E.G. demonstrates a rhythmic bilaterally synchronous three per second spike and wave rhythms during the interictal period. There is often a familial tendency and usually manifests itself in the first twenty years of life. *Focal epilepsy* arises from a localized epileptogenic focus within the cerebral cortex and includes psychomotor epileptic seizures. In this category, the E.E.G. usually gives evidence of a localized disturbance, and, clinically, the beginning or onset of the seizure discharge gives a clue as to the localization of the epileptogenic focus. *Idiopathic epliepsy* describes those seizures where there is no significant macroscopic lesion detectable after extensive neurological investigation. These cases may have either a focal or generalized onset, and the E.E.G. recording may either be normal, show a localized disturbance, or demonstrate a generalized non-specific disturbance. Many authors do not restrict the idiopathic type to genetic, centrencephalic or highest level seizures. Some people, however, use the term idiopathic epilepsy as synonomous with petit mal. *Symptomatic epilepsy* refers to those seizures where a cause has been elucidated after neuroradiological investigation.

ORIGIN OF EPILEPTOGENIC FOCI

The focal cortical seizures necessarily arise focally within the cerebral cortex. The origin of genetic, essential, or what Penfield calls centrencephalic or highest level seizures has recently been disputed. Penfield[14] states that the probable site of origin is in the higher brain stem or 'centrencephalon'. He[15] defines centrencephalic as the 'neurone systems which are symmetrically connected with both hemispheres and which serve to co-ordinate their function. These circuits are located in the brain stem. This would include the thalamus with the diencephalon, also the mesencephalon, and the rhomboencephalon'. However, recent experimental evidence has questioned this area as the origin.

Stevens[20] and co-workers found that they had to make relatively large lesions in the mid brain tegmentum before they could induce by flickering lights, seizures in cats. They stated that their findings did not permit them to conclude that the origin of essential epilepsy was in the brain stem. They quoted the works of other authors who did not observe any spontaneous seizures in normal cats following large destruction of midbrain tegmentum. White,[23] in his recent study on 44 adult patients who had brain stem tumours, does not mention epilepsy as a neurological symptom in any of his cases. There were three cases who had brief alterations of consciousness. Other studies note the lack of correlation between diseases of the brain stem and epileptic seizures. William's[27] eloquent article draws heavily upon experimental and clinical evidence to conclude that there is little proof to consider the centrencephalon as the site of origin of generalized epileptic attacks. He states that the 'thalamic intralaminar structures' are most probably involved in the mediation of epileptic seizures which arise elsewhere in the brain. Indeed, there must be an intact diencephalic mechanism in order for an epileptic attack to become generalized. He cites clinical evidence that some patients with extensive mid brain damage, although they may have focal seizures, have never had a generalized convulsion.

At the present, it is impossible to implicate any specific brain area as the site of origin of essential or genetic epilepsy. It may indeed be a manifestation of some generalized dysfunction involving some chemical, metabolic, or structural factor. The hereditary predisposition prevalent in some cases of essential epilepsy may be the result of the transfer of some undetermined factor by genetic mechanisms.

The localization of site of origin of idiopathic epilepsy, using the term in its broadest sense, remains a controversial point. It is possible that the modern diagnostic tools of investigation are not precise enough to demonstrate some small epileptogenic focus. This problem is particularly illustrated in cases of idiopathic epilepsy with a focal onset.

Thus, when considering both essential (genetic) and idiopathic epilepsy which have unconsciousness as their initial manifestation, it is difficult, indeed impossible, to define the site of origin either as a focal lesion in a silent area of the brain such as the prefrontal cortex, or as a diffuse unlocalized disturbance in the cerebral cortex. Focal lesions may have loss of consciousness as the initial manifestation but this is rare.[14] Essential (genetic) epilepsy which has a familial tendency in some cases may arise as a consequence of certain maturational and metabolic factors not yet defined nor considered to be important.

CLASSIFICATION

Any classification of epilepsy must be simple and useful from the standpoint of clinical usage.[13] Furthermore. it should take into consideration such factors as anatomy, etiology, symptomatology, and functional disability. A number of classifications have been presented by different authors and each has its limitations.[11] A modification of a classification described in Epilepsia will be presented.

EPILEPSY OF LATE ONSET

Epilepsy of late onset describes those cases in which the initial epileptic seizure occurred after the age of 20 years.[3] The relative paucity of literature upon this topic makes it very difficult to establish with certainty the relative frequency of the various symptomatic causes, the proportion of cases classified as idiopathic, the incidence, and the prognosis. In each review of this topic, the author excludes certain groups of symptomatic causes from their series. Therefore, it is with these reservations in mind that the following data is presented.

Site

One of the most important and fundamental questions in neurology is the location of the lesion. Most authors agree that a convulsion, whether the cause is extracerebral or due to cerebral disease, is, on the whole, a direct and specific response of the cerebral hemispheres to either physiological disturbances or pathological damage. Epilepsy[27] is a symptom indicating the specific vulnerablity of the cortex for spontaneous disorderly electrical discharges not shared by the rest of the neuraxis. Indeed, the lowest thresholds to the production of convulsions by chemical and electrical means were found in the fronto-tempero-parietal regions, higher in subcortical regions and the highest in the remainder of the neuraxis.

Lesions of the rolandic and parietal regions are more prone to produce seizures than elsewhere in the neuraxis. Tumours which are nearer the rolandic zone, especially the lower end, give rise more frequently to seizures. Superficial tumours are more prone to produce seizures than deeper lesions. In an analysis of 222 highly selected cases of focal cerebral seizures, Penfield[14] found that motor and sensory phenomena occurred most frequently as the initial phenomena.

Incidence

Epilepsy occurs quite commonly in man. The overall incidence has been reported to be 6-7/1000.[2] However, there is a great divergence of opinion with regard to the frequency of epilepsy of late onset. Some authors believe that epilepsy rarely occurs after the age of 20.[8] Most authors quote under 25% of all epileptic patients whose seizures start after the age of 20.[18] Alajouanine et al[1] analyzed 7,745 cases of epilepsy from the literature between 1901 and 1955 and found a 32.7% incidence of epilepsy starting after the age of 20.

Sex and Age

Gower[6] considered that before the age of 30, females had a higher incidence of having epileptic seizures and that after 30 years of age, this relationship was reversed. Furthermore, epilepsy beginning after the age of 60 occurred almost exclusively in males. In a more recent review on epilepsy after the age of 50, there

Group	Anatomy	Etiology	Symptomatology	Functional
1. Essential (genetic)	Brain as a whole	Unknown	grand mal petit mal	Varied
2. Focal (a) Known cause (b) Unknown cause (idiopathic)	Area	Varied	Varied	Varied
3. Unlocalized* (a) Known cause (b) Unknown cause (idiopathic)	Brain as a whole	Varied	grand mal	Varied

*Will include those cases where the cause of the seizure was unknown prior to investigation but subsequently was ascribed to an extracerebral cause like hypoglycemia, hypocalcemia, etc. These patients are not strictly epileptics but have hypoglycemic convulsions, hypocalcemic convulsions, etc.[26]

was no male predominance, the ratio being almost 1:1 male to female.[28]

In Raynor et al series,[18] approximately 90% of seizures occurred between the ages of 20 - 50 years of age. There didn't appear to be an appreciable difference in frequency between the third, fourth and fifth decades. Thereafter, the incidence dropped precipitously with the majority of cases occurring in the age group from 50 - 59 years. However, epilepsy may have its initial appearance in the 7th and 8th decades.

In Dimsdale's series of 200 cases,[3] 60% of her cases had their first seizure before the age of 40 years.

Predisposing Factors

Psychogenic disturbances have been considered to play a role in the production of seizures, if not as an aetiological agent, then as a precipitant of a convulsion.[9] Indeed, adverse emotional situations may lower the convulsive threshold to a level which facilitates the precipitation of convulsive seizures. Fright may be a potent exciting cause in women past the age of 20 in some cases.[7] In one series,[4] 40% of their cases of late onset epilepsy showed severe, and unequivocal emotional strain. However, the role of emotional stress and psychiatric illnesses may be considered still ill-defined, because of little experimental verification.

Baker[2] quoted the works of Lennox who was of the opinion that there may be a hereditary predisposition in those patients who have symptomatic epilepsy. The finding of a direct correlation of epilepsy with tumour types and the rapidity of their growth casts doubts on the role of hereditary factors in symptomatic epilepsy. It is probably minor.

Type of Seizure Pattern

The most common seizure pattern in late onset epilepsy is generalized (non-focal) seizures. Livingstone,[9] who excluded brain tumours and acute cerebral diseases from his series, reported an incidence of 77.5%; Raynor and co-workers,[18] who excluded all with a history of febrile convulsions in childhood and all post-traumatic epilepsy, 71%; Martin and McDowell,[10] 77.5% in an unselected series. The remaining cases in each series had initially a focal onset which subsequently in some became generalized.

ETIOLOGY

1) Tumours

It is a well established fact that brain tumours have been associated with epileptic seizures. Penfield and co-workers[12] found that epilepsy was frequently one of the symptoms of brain tumours. Seizures occurred in 37% of intracerebral tumours and in 45% of extracerebral supratentorial neoplasms. It may be the initial symptom in a substantial number of cases between 20-40%. There was a direct correlation between the chronicity of growth of the tumour types and the seizure incidence as well as the percentage frequency of seizures as the first symptom. Their analysis of seizure incidences revealed that epilepsy occurred in 70% of astrocytomas, 92% of oligodendrogliomas, and 67% of supratentorial meningiomas, while in only 37% of glioblastomas, the most malignant of the glioma group. The incidence as the initial symptom showed a similar distribution 60%, 75%, 62% of astrocytoma, oligodendroglioma, supratentorial meningioma respectively verses 37% for rapidly growing glioblastoma group.

The frequency of tumours as the cause of recurring seizures is comparatively small. In a large general hospital clinic, intracranial tumours may be present in 5 - 10% of all patients suffering from seizures.[24] The percentage to total in late onset epilepsy is approximately 15%. Baker cites 14%,[2] Raynor and co-workers,[18] 13.6%; Dimsdale,[3] 19% excluding angiomas and 23% with their inclusion. The latter two studies excluded post-traumatic epilepsy from their analyses. Tumours may account for one third (33%) of focal seizures evolving after the age of fourteen.[21]

Focal seizures occur more frequently than generalized attacks in those cases of late onset epilepsy associated with tumours. The axiom that focal fits are indicative of a tumour is not borne out by clinical studies. Vascular disease which is associated with late onset epilepsy may give use to focal seizures in a large percentage of cases.[21]

Epileptic seizures associated with an intracranial neoplasm occurs more frequently before the age of 50. In a highly selected series of focal seizures produced by brain tumours, Rasmussen[17] found the majority of their cases had their onset of seizures in the third decade or later. The median for their cases of oligodendioglioma, astrocytoma, glioblastoma multiforme, and meningioma were 28, 29, 38, and 42 years of age respectively. However, late onset epilepsy after 50 does not rule out statistically the probability of demonstrating a neoplasm. The incidence has been reported between 9[25] - 36%[18].

Metastatic tumours to the brain may give rise to late onset epilepsy in about 30% of cases.[19] Although metastatic growths constitute approximately 5% of all expanding intracranial processes of all ages, their frequency may reach as high as 25% between the ages of 40 to 60 years. Furthermore, in those patients whom such growths produce epileptic seizures it may be the initial symptom in 25% of these cases.

The problem in making a positive diagnosis of a brain tumour as the cause of late onset epilepsy may be exceedingly difficult in some cases. This is especially illustrated in those cases where the growth of the seizure producing tumour is so slow that it may be present for years without being associated with, any

neurological deficit or symptoms and signs of increased intracranial pressure.[17] Many such cases have been treated for years as ordinary (idiopathic) epileptics. Thus the duration of seizures does not in itself rule out the presence of a neoplasm. If a tumour is present in such cases it will probably be a slowly growing glioma, usually an astrocytoma. Because a seizure producing brain tumour may mimic idiopathic epilepsy, the investigation of all patients with late onset epilepsy must be extensive and complete.[5 17]

2) Vascular Disease

Generalized vascular disease is the most frequent presumptive cause of epilepsy after the age of 50.[13] The incidence has been reported as high as 32% of cases of late onset epilepsy past 50 years of age,[18] and as frequent as 62% of all cases of focal seizures beginninig after 50 (being twice as common as brain tumours).[21] These conclusions are not valid if consideration is given only to those cases with no neurological symptoms or signs preceding the onset of seizures and with no previous history of epileptic seizures. With this degree of selection, an intracranial neoplasm will be the presumptive cause more frequently than vascular disease regardless of the type of seizure pattern.[28] Focal and generalized seizures occur with about the same frequency.

3) Miscellaneous Causes

Many cases of late onset epilepsy are due to causes which, if considered individually, occur relatively infrequently, but, as a group constitute between 10-15% of all cases of late onset epilepsy. Such cases include diabetes, brain abscesses, cerebral atrophy, granulomas, subdural hematomas, burnt out tabo-paresis, post-traumatic seizures, and even birth lesions.

Between the ages of 18 or 20 and before 35 years, head trauma and injury is the most frequent cause of epilepsy.[13] However, the relative frequency of post-traumatic epilepsy in late onset epilepsy has not been studied and thus no overall conclusions may be reached. A person who has sustained a head injury will develop epilepsy three times more frequently if there is dural penetration.[22] Furthermore, the possibility of epileptic seizures secondary to subdural hematoma or brain abscess must be ruled out.

Birth lesions may produce epilepsy for the first time after the age of 20.[16] Lesions involving the temporal lobe especially the infero-mesial zone are particularly the site of origin of the epileptogenic foci. Congenital lesions, like agenesis of the corpus callosum, may be associated with late onset epilepsy.

4) Idiopathic Epilepsy

There are a substanial number of cases of late onset epilepsy where after extensive investigation no significant macroscopic lesion is detected nor appeared after a five to ten year follow up.[9] These cases are not restricted to essential or genetic epilepsy. The type of seizure pattern may be generalized (unlocalized) or focal. One series reported the percentage of each as 86% and 14% respectively.

Idiopathic epilepsy constitutes a large percentage of all cases of late onset. Dimsdale[3] reports an incidence of 55% in her series which excludes post-traumatic cases and those cases with papilledema; Livingstone,[9] 78% in his series which excluded brain tumours and any acute disease; Woodcock et al,[28] 26% of his cases whose epilepsy started after the age of 50; Sumi et al,[21] 15% of focal seizures commencing after the age of 20 years.

In the majority of cases of idiopathic epilepsy, there may be found some non specific abnormalities in the electroencephalographic tracings.[9] However, the pneumoencephalogram and clinical examination are almost invariably normal.

INVESTIGATION

The most perplexing question is the extent of investigation to be carried out on each patient who presents with late onset of epilepsy. This problem is especially diifficult in the patient who presents having a history of a single seizure and a negative neurological examination.[17] There is great variation in opinion among different authors.

Rasmussen[17] feels that any person past the age of 20 who has had a single seizure should be fully investigated as soon as possible. It is his experience that a significant number of such patients will have a brain tumour which, if not detected after the first investigation, will be demonstrable in time. He considers that a negative pneumogram on the first full investigation doesn't rule out the diagnosis of a tumour but indicates that at this time, there is no evidence of a neoplasm. Furthermore, a negative study will act as a base line to detect even the most insignificant change should a second full investigation be indicated by a change in the status quo of the patient. He feels that the patient with a negative study should be followed at monthly intervals in a neurological clinic where periodic electroencephalograms can be made. He has found that a substantial number of such patients will have a demonstrable brain tumour.

Martin and McDowell[10] feel that 'regardless of the type of seizure, the E.E.G. rarely indicates the presence of an intracranial mass lesion when there is a negative bedside neurological examination. Further, irrespective of age of onset of generalized seizures, if the bedside neurological examination fails to indicate evidence of focal brain dysfunction, an encephalography at that moment is not likely to demonstrate a mass lesion. Regardless of age of onset, if the seizures are focal, an encephalography is likely to indicate the presence of an intracranial mass lesion, despite a negative neurological examination.'

Raynor and co-workers[18] listed four criteria as a proper indication to investigate fully to rule out the possibility of brain tumour.

1. The presence of abnormal physical neurological signs.
2. The occurrence of seizures of focal motor character or with focal sensory aura.
3. The presence of focal abnormality in the E.E.G.
4. Initial onset of epilepsy after the age of 50 years.

In all of their cases in which they found a brain tumour to be the cause of late onset epilepsy, at least one of their four criteria had been previously satisfied. In the majority of cases, at least two were present. They considered the presence of abnormal physical signs is the best single criteria to diagnose tumours. Their presence indeed increased significantly the probability of finding an intracranial neoplasm.

They considered that those cases with a normal pneumogram, should be followed for a three year period. If during that time no adverse developments occurred, this was probably sufficient to rule out a brain tumour. However, a follow up study for fifteen years is probably necessary to rule out a tumour in those cases where a pneumoencephalogram was not performed.

Dimsdale[3] concludes that a full neuroradiological investigation is advisable in those patients whose epileptic attacks began after the age of 40, are focal, have been present for less than five years, or whose attacks are associated with physical signs or a bruit. She believes that E.E.G. coupled with a pneumogram is the most suitable mode of investigation and angiography be restricted to those cases with prominent lateralizing signs or a bruit.

In conclusion, ideally it would be advisable that all cases of late onset epilepsy be investigated fully and to follow at monthly in a neurologic clinic those patients who had a negative study. When facilities for such extensive investigation are not readily available, the criteria for full neuroradiological investigation outlined by Raynor and co-workers or by Dimsdale should be followed to screen which patients to be sent to a neurological clinic for investigation.

Prognosis

Most authors consider that late onset epilepsy has a favourable prognosis unless it is caused by an intracranial tumour.[8 25] Seizures commencing after the age of 45 years tend to occur very infrequently.

SUMMARY

Epilepsy is a symptom denoting primary cerebral dysfunction. The present terminology to discuss the parameters of cerebral seizures is confusing. A distinction must be drawn between essential (genetic, centrencephalic, highest level seizures) and idiopathic epilepsy. The former manifests itself before the age of 20, and is grand mal or petit mal in type. The latter may manifest itself at any age and may be focal or generalized in presentation. The site of origin of essential epilepsy is unknown at the present time. Recent evidence points away from the upper brain stem towards a diffuse cerebral disturbance of unknown nature. Maturational, genetic, metabolic, chemical or structural factors may be involved but are not yet defined. There is still no universal agreement as to an appropriate classification of the epilepsies. The older concept of classifying by seizure type either grand mal, petit mal or psychomotor seizures is no longer tenable for such a classification ends before its usefulness begins.

Epilepsy of late onset describes those cases where the seizures start after 20 years of age. The incidence of late onset epilepsy is probably under 25% of all cases of epilepsy. The majority of cases have their initial seizure episode before the age of 50. The role of psychogenic disturbances as a predisposing factor to seizure discharges may be of importance but at the present, ill-defined.

Epilepsy is frequently one of the symptoms of brain tumour. It occurs more frequently in the symptomatology of slowing growing intracranial masses than the rapidly growing glioblastomas. Epilepsy may be the initial symptom which heralds the presence of a brain tumour, especially slowly growing neoplasms. The frequency of tumours as the cause of seizures after 20 is approximately 15%. Metastatic tumour to the brain not infrequently give use to epileptic seizures.

Idiopathic epilepsy constitutes a substantial proportion of all cases of late onset epilepsy. However, some of these cases may represent the latest phase in the course of development of a brain tumour. Seizure producing brain tumours may be present for years without any other symptomatology nor physical signs. The problem of the extent of neuroradiological investigation has to be considered. One author feels that all cases of late onset epilepsy should be investigated while others are selective along the lines of certain criteria. The prognosis of a patient with late onset epilepsy is favourable unless the actiological agent is an intracranial neoplasm.

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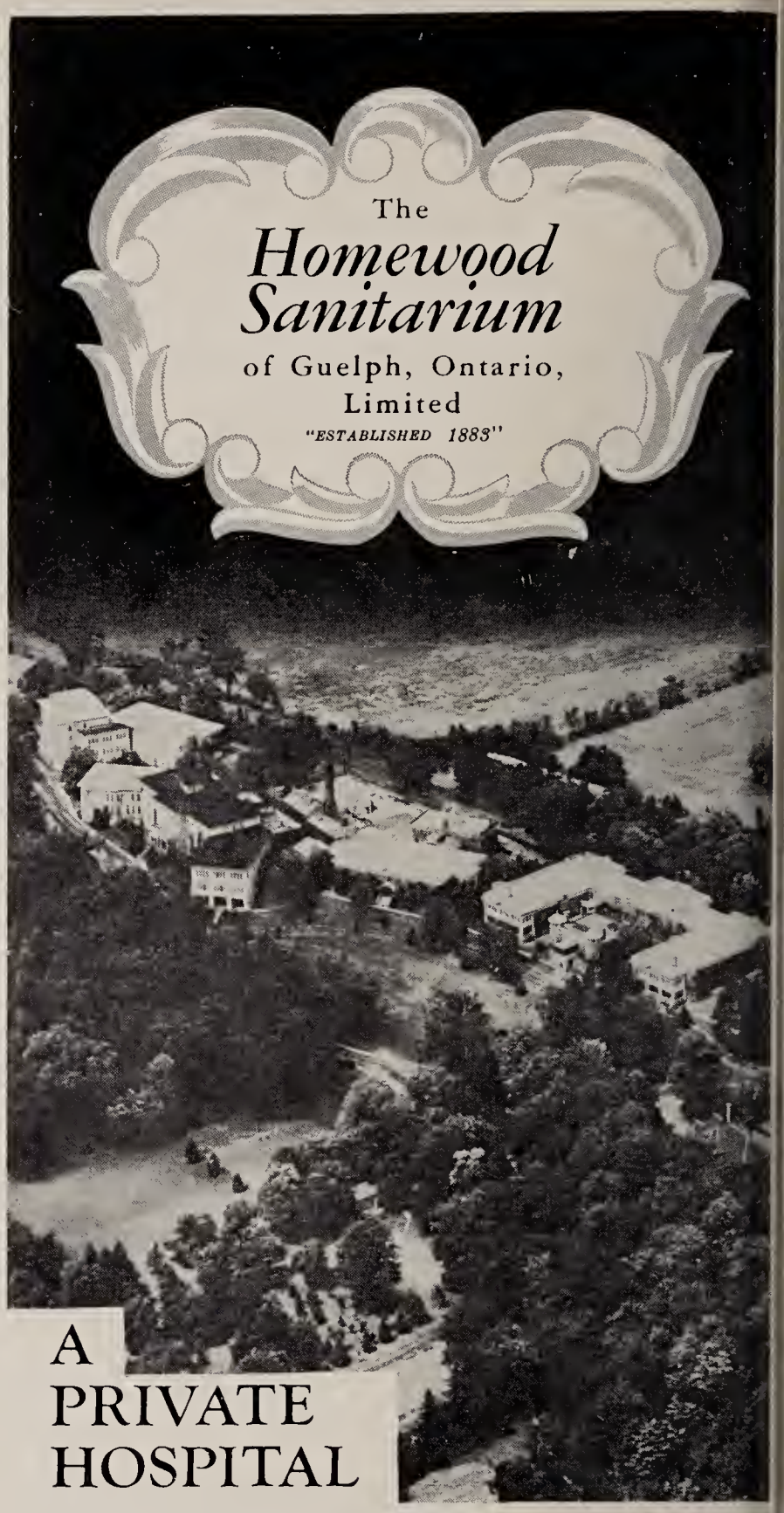

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The Unconscious Patient

H. Shulman 6T6

The physician who assumes the responsibility for a comatose patient is faced with two problems.

1. The patient must be kept alive and disabling sequelae prevented — such as permanent cerebral damage.

2. The underlying disorder must be uncovered and appropriate measures applied.

The purpose of this article is to review the early management of the unconscious patient and to suggest a method of diagnostic evaluation.

CLASSIFICATION OF COMA (Modified after Harrison[9])

No focal signs No CSF changes	No focal signs CSF changes present	Focal signs ± CSF changes
A. Intoxications	• Meningitis	• Head injury
B. Metabolic disturbances	• Subarachnoid hemorrhage	• Intracerebral hemorrhage
C. Infection (systemic)		• Infarct
D. Circulatory collapse		• Space-occupying lesion
E. Post-ictal		
F. Hypertensive encephalopathy		
G. Thermic		
H. Hysteria		

PHYSIOLOGY

The reticular formation is a pool of neurones extending from the upper end of the spinal cord into the thalamus, where it joins the thalamocortical projection system, i.e. it forms the core of the brain stem. In addition to its role in complex reflexes (swallowing, sneezing, coughing), and the regulation of respiration and circulation, it has the ability to activate the cerebrum. The portion of the reticular formation concerned with this activation (i.e. the maintenance of consciousness) is called the ascending reticular activating system (ARAS). In an unconscious patient, the ARAS has been affected in one of four ways:

1. Directly e.g. trauma or ischemia due to brain stem infarction
2. Indirectly e.g. pressure from a lesion or cerebral edema
3. Diffuse disease e.g. uremia
4. Toxins acting directly on the ARAS e.g. tranquilizing drugs

DEFINITIONS

The progression from consciousness to deep coma has been divided into many stages. For therapeutic purposes, three stages are sufficient.

Stupor—a state in which physical and mental activity is minimal. The eyes may be open and the patient may look at the examiner, but response to command is absent, slow or inadequate. If the eyes are closed, the patient can be roused when shaken vigorously or called by name but is irrational and lapses back to unconsciousness.

Light coma (semi coma)—most reflexes are present and the patient may stir or moan when pinched or shaken e.g. the facial muscles will contract on supraorbital pressure.

Deep coma—there is no response to stimulation. Most reflexes are absent (tendon, pupillary, corneal), respiration is often slow or Cheyne-Stokes in nature, and the pupils are usually fixed and dilated (exceptions are certain drug poisonings and pontine hemorrhage).

Akinetic mutism (coma vigil)—is a rare state in which the patient appears alert, with eyes open, but neither moves nor speaks—and cannot be roused by peripheral stimulation. It is seen occasionally in lesions of the brain stem affecting the reticular formation.[14]

The patient who falls into the comatose category—whether stuporous or in deep coma—will have lost some or all of his protective reflexes. It is then up his attending physician to anticipate his internal needs and institute corrective and often lifesaving measures.

EARLY MANAGEMENT

1. Airway

1) *Outside hospital*—your first concern is to clear and maintain an adequate airway with the patient in the

lateral position. If you suspect a spinal injury and are afraid to move the patient without assistance, at least turn his head to the side. If you suspect a cervical injury, apply neck traction while turning the patient. Never leave the patient flat on his back.

Look in the mouth, remove dentures, debris and food, then palpate with your finger. Keep the head extended and in the lateral position. If necessary, begin mouth to mouth respiration. An oropharyngeal airway, if available, should be inserted. *Do not leave the patient alone.*

2) *In hospital*—quickly assess the respiratory state. If indicated, insert an endotracheal tube and have a nurse ventilate the patient with an Ambu bag until a respirator is available.

Whether intubated or not, suction the patient with a soft, sterile, rubber catheter. Use a syringe if suction not immediately available.

The comatose patient will not usually need intubation and the rest of the examination should be continued, returning later to re-assess the respiratory state. However, it is often advisable to leave in an oro-pharyngeal airway. The only sure method of knowing if ventilation is adequate (cyanosis sometimes being unreliable[4]) is by determining arterial pH, pO_2, pCO_2 and O_2 saturation.[5] Femoral arterial puncture is simple, and if finger pressure is maintained at the site for five minutes, post puncture bleeding is negligible.

Later, if you suspect that the coma is going to be prolonged, or, if you suspect some degree of respiratory obstruction, or if an operation is necessary (e.g. head injury), an *elective* tracheotomy should be carried out. This is a simple hospital procedure and can often be lifesaving as it decreases dead space, makes secretion removal more effective and facilitates the application of a respirator and oxygen. The inspired air should be humidified to prevent drying and predisposition to infection. Don't wait for chest signs to develop before deciding to do a tracheotomy.

2. Circulation

Vital signs—check the pulse (femoral, carotid, radial) and listen to the heart. Loosen tight garments. If in cardiac arrest, start external massage—alternating with mouth-to-mouth respiration if necessary.

Shock

1) *Outside hospital*—place in shock position and maintain a clear airway. Keep warm and control bleeding with direct pressure. Give nothing by mouth (the patient may aspirate, or an anesthetic may be needed later).

2) *In hospital*—treat the shock according to its etiology, e.g. if hypovolemic secondary to bloodless, insert an indwelling venous catheter, withdraw 30 cc of blood (send 20 to the lab., and keep 10 cc unclotted blood—See V) and start an infusion of dextran while waiting for the blood.

If IV therapy is going to be maintained and the patients cardiovascular status is questionable, a central venous pressure outfit is the best indicator of the circulatory load.

An indwelling urethral catheter should be inserted to follow urine output (especially if on IV therapy), have samples available for analysis and to prevent skin ulceration.

3. Cerebral Edema

One of the major causes of death of the unconscious patient is cerebral edema (due to trauma, inflammation, hypoxia). This dangerous state is predisposed to by the increase in blood volume resulting from cerebral vasodilatation due to accumulation of CO_2. Although a healthy brain can tolerate extreme hypotension if the fall is gradual and the blood vessels healthy, the brain deprived of nutrients (glucose and O_2) for more than three minutes (eg. due to aspiration) suffers irreversible cellular damage[7] and the resulting cerebral edema can be permanently damaging or fatal. For this reason, the unconscious patient requires constant nursing attention and a suction apparatus at the bedside.

If there is evidence of cerebral edema (progressive coma; fixed, dilated pupils; papilledema; rising blood pressure with bradycardia) certain measures should be taken. The following measures are instituted after the patient has been admitted.

1. Hypothermia

Using a special 'apparatus', maintain the temperature between 30 and 35° C (below 30° C, arrhythmias may develop). This lowers the BMR, decreases basal oxygen requirements and minimizes brain damage.

If the patient starts to shiver (thus raising the body temperature), chlorpromazine may be of help. Take readings every hour (rectally).

2. Osmotic Diuretics

Administer Mannitol (20% solution). A test dose should be given first (100 cc as fast as possible) to check if renal function is adequate and prevent pulmonary edema. If more than 100 cc of urine is put out in the next hour, 500 cc of 20% Mannitol can be administered every twelve hours. If there is no improvement within a day or two, it is probably not going to help.

Watch for dehydration, electrolyte disturbances and oliguria. Intracranial bleeding must be ruled out before Mannitol is administered (arteriogram, burr holes).

3. Steroids

Besides being anti-inflammatory (and decreasing cerebral edema), steroids increase the glomerular filtration rate.

Dexamethasone (Decadron(R))
—10 mg IM stat
—4 mg q12h for 2-3 days, then taper.

4. History — see Diagnostic Evaluation

5. Laboratory

As soon as the blood has been taken send it to the lab. for:

—venous (20 cc):
—Hb; Hct, wbc, differential
—electrolytes, BUN, Glucose
—barbiturates, bromides and salicylates
—Type and Cross, if indicated
—Ca^{++}, P, Doriden & alcohol levels if indicated
—The 10 cc of blood you keep may come in handy later for a serum level of a substance not initially suspected.
—arterial (20 cc): —pH and blood gases.

DIAGNOSTIC EVALUATION

History

While the emergency management is being carried out, someone should be delegated to question witnesses or relatives, and look through clothing (and wallet) for names of relatives (or Doctor), evidence of medication and special cards, eg. diabetic, anticoagulant. The following questions should be asked:

—Have there been any previous similar episodes?
—Is there a history of epilepsy, diabetes, alcoholism or trauma?
—Has the patient been in hospital before? Why?
—Did you witness the episode? Describe it.
—Under what circumstances was the patient found?
—Any suicidal tendencies?
—Was the patient on any medication? (ask specifically re: sleeping pills, tranquilizers, etc.)

As evidence arises from the physical evaluation of the patient, ask questions relating to specific disorders (eg. renal, hypertension, hepatic.)

Physical Examination

The following scheme is not suggested as a rigid plan of investigation but as a guide to the signs one should look for when time is limited and an early diagnosis may be life-saving. In the first few minutes only part of it would be carried out, the rest of the investigation being completed after the patient is out of immediate danger.

A. Observe

—body position, head position, unilateral facial movements
—respiration
—marks on clothes (eg. burns) or signs of trauma

B. Assess the level of consciousness

—what is the patients response to shaking, deep pressure (supraorbital and achilles tendon) and reflexes—especially corneal and pupillary.

C. Examine

1) Head

General
—colour of face; facies
—signs of injury (blood, bruises, CSF leakage)
—palpate for depressed fractures — including spine
—cranial bruits

Eyes
—pupil size, equality, reaction to light
—ocular tension
—any deviation; if stuporous, test for hemianopia by quickly bringing your hand in from the side
—conjuctiva for anemia, petechial hemorrhages
—funduscopic

Neck
—stiffness (may be masked in deep coma)
—carotid bruits

Breath
—alcohol, acetone, uremia, fetor hepaticus

2) Cardiovascular
—heart rate, rhythm, murmurs
—blood pressure

3) Respiration
—rate, depth, rhythm; Kussmaul? Cheyne-Stokes? Biot?
—cyanosis, clubbing
—position of trachea
—evidence of infection (auscultate)

4) Skin and extremities
—temperature, colour, rashes petechiae
—palmar erythema, needle marks
—palpate limbs and ribs for fractures

5) Neurological — this is often done first as it gives you an indication of the level of consciousness and often the diagnosis.

i) Eyes
—size, equality, reaction to light
—funduscopic (do not dilate eyes as this removes an important diagnostic and prognostic sign)

ii) Tone
—Opisthotonus and/or extension of all extremities is a sign of decerebrate rigidity

and indicates a disorder of upper pons or midbrain (eg. hemorrhage, basilar occlusion, pressure cone), or occasionally a drug effect (eg. phenothiazines)
—Complete flaccidity may indicate a specific poisoning or it may be due to the spinal shock or cord transection.
—Increased tone may be due to a new or old stroke. In early stages of stroke, the limbs may be flaccid.

iii) Paralysis
—look for unilateral facial movements (eg. puffing out cheek on expiration) and if restless, unilateral limb movements. Check for paralysis of the tongue and palate (gag reflex).
—stimulation of both achilles tendons (separately) may result in repeated withdrawal of the same limb, suggesting paralysis of the other limb. Similarly, supra-orbital pressure (both sides) may result in movement of only one upper limb. Occasionally, the results of this stimulation may suggest a lesion level.

iv) Neck rigidity
—this may be due to meningitis, subarachnoid, or intracerebral hemorrhage. Rule out cervical spine disease.

v) Reflexes
—Deep tendon reflexes are occasionally decreased in the early phase of an acute lesion and absent in deep coma. However, there is a great deal of individual variation, so that deep reflexes should not be relied upon as an indication of the level of consciousness.
—Superficial reflexes —
extensor plantar responses do not necessarily mean a destructive brain lesion. They may be present in any comatose patient. Absent corneal reflexes are a poor prognostic sign.

The above are the conventional tests done on the unconscious patient. There are rare occasions when the information obtained may be misleading, eg. the corneal reflex can be absent in hysteria or catatonia and psychotics may fail to respond to noxious stimuli. The following tests are then of added value.

1. Oculocephalic reflex — when the head is passively turned to one side, the eyes deviate to the other side. Absence of this reflex indicates either deep coma, or a severe brain stem lesion.[12] If absent to one side, it has localizing value, and if only one eye is affected, it may indicate a third nerve palsy. Occasionally, the oculocephalic reflex reveals a nystagmus when the eyes are forced into lateral gaze. This may be the only clue to barbiturate poisoning.[12]

2. Caloric test — syringing the ear with ice-cold water produces the following ocular responses.[12]

1) tonic conjugate deviation toward the side of stimulation in light coma

2) disconjugate or dissociated ocular movements in brain stem diseases

3) no response in deep coma

3. EEG — is helpful in differentiating sleep, stupor, coma and catatonia, as well as revealing local dysfunction and seizure patterns.

With the exception of the last two tests, the above neurological examination can easily be done in a minute or two. An additional minute is sufficient to check breath, skin and auscultate the heart and lungs. The results of this brief examination are usually sufficient to suggest the diagnosis in 80% of cases. Eventually, as complete as examination as possible should be done, checking especially for sites of primary neoplasms (lungs, abdomen, testicle).

Laboratory and Special Tests

1. Blood—see Early Management -II-

2. Urine—S.G., protein, pH, glucose, albumin, acetone
—microscopic
—specific tests where indicated (eg. for drug excretion)

3. Lumbar puncture
—should be done early unless contraindicated (any signs of increased intracranial pressure). It should be done immediately if meningitis or subarachnoid hemorrhage is suspected.
—pressure, colour and turbidity, Gram stain, pellicle, culture
—protein, glucose cells, xanthochromia

4. Echogram — if head injury suspected, to reveal shift of midline structures.

5. X-rays

1) Skull
—plain — look for shifted pineal, intracranial calcifications, metastases (blastic or lytic changes), skull fractures and subdural hematoma.
—Angiography — this is not an emergency procedure, but in cases of suspected intracranial hematoma or neoplasms, it should be done early as the lesion may be amenable to surgery.

2) Chest
—look for tumour or infection.

3) Others
—plain films of abdomen, skeletal survey.

6. Other tests — eg. ECG.

DIFFERENTIAL DIAGNOSIS

The following classification is of diagnostic value as it uses evidence that arises from your evaluation—focal or lateralizing signs and/or CSF findings — to divide the most important causes of coma into 3 major groups (see Table 1). A more complete classification may be found in various texts.[16]

1. *No Focal Signs No CSF Changes*

A) Intoxications

i) Alcohol — responsible for 40-50% of admissions

The chronic alcoholic often has signs of liver disease as well as an alcoholic or "stale" breath, coated tongue, flushed face and injected conjunctiva. The eyes may be dilated and tachycardia with hypotension are usually present. Calf pressure may evoke signs of tenderness (withdrawal) as a result of low-grade peripheral neuritis.

If the patient has ingested methyl (wood) alcohol, there may be a history of previous headache, blindness or abdominal pain. This patient often presents in severe acidosis with fixed dilated pupils.

Because of the frequency of subdural hematomata developing in alcoholics, usually as a result of a fall, the diagnosis of alcoholic coma must be made by exclusion.

ii) Barbiturates—responsible for 20-30% of admissions

Barbiturate intoxication is characterized by flaccid coma, hypothermia and hypotension. The pupils are usually constricted but may be dilated and non-reactive. In severe intoxication, respiration is slow and shallow or irregular, deep tendon and corneal reflexes are gone and the plantar responses are often extensor.

The short acting barbiturates produce a rapid brief coma (less than 24 hours) whereas the long acting are slower in onset and last longer (up to four days). The picture may not be clear cut because of 'combination' drugs. One should also be alert to the possibility of simultaneous alcohol and drug intoxication presenting without definite signs of either.

iii) Opiates

Coma is characterized by shallow respiration, bradycardia, hypothermia and pinpoint pupils (except meperidine). In the most severe degrees of intoxication, the pupils may be dilated.

Investigation for drug-induced coma includes history (previous intake, medications, suicidal tendencies), search of clothing, drug levels (serum and urine), and gastric analysis. Look for needle marks.

B) Metabolic Disturbances

1) Diabetic acidosis

The history may include gradual onset of thirst, nausea and vomiting, abdominal pain, drowsiness, stupor and fever. Examination reveals a flushed, dehydrated patient, Kussmaul respirations, 'fruity' breath and decreased ocular tension. Hypotension and bradycardia are often present and funduscopic examination will occasionally reveal diabetic retinopathy.

Look for signs of infection as this is often a precipitating factor.

Laboratory work reveals elevated serum glucose and ketones with glucosuria and ketonuria. The arterial pH is decreased and the CO_2 content is less than 10 mEq/L (exception is hyperosmotic non-ketotic diabetic coma[20]). Do not rely on dextrostix or urinalysis only. Large cerebral infarcts or hemorrhage may result in elevated blood sugar, but there is no elevation of ketones and focal signs are usually present.

2) Hypoglycemia

The onset is rapidly progressive and a history of palpitations sweating, headache and diplopia preceding the coma is often obtainable.

Examination reveals a pale, sweaty skin; full, bounding pulse with normal or increased blood pressure; and normal or shallow respirations. The pupils may be dilated and a funduscopic examination may reveal retinopathy. The ocular tension is normal, but the plantar responses may be extensor.

Laboratory—the blood glucose is less than 50 mg% and there is no glucose in the second urine specimen. The diagnosis is confirmed by immediate relief of symptoms following IV administration of glucose.

Note: The unconscious diabetic in hypoglycemia may present as transient hemiplegia, aphasia and/or convulsions. Therefore, always do a blood sugar, even if the diagnosis is an 'obvious' stroke.

3) Uremia

There may be a history of renal disease. Advancing uremic coma is characterized by anemia, headache, vomiting, diarrhoea, pruritus and twitching.

Examination reveals a dry, 'sallow' skin, and fetid ammoniacal breath. Breathing is usually Kussmaul because of the acidosis (Cheyne-Stokes terminally) and tetany may develop. Pulmonary edema is frequently present and a pericardial friction rub is heard in the later stages. Retinal hemorrhages and exudates are usually present to some degree.

Laboratory—BUN and creatine are elevated. CO_2 content is decreased (as is Ca^{+2}) and K^+ is increased.

4) Hepatic coma

The commonest causes are portal cirrhosis, post hepatitic cirrhosis and post-caval. Precipitating factors (in cirrhotics) include GI bleeding, alcohol and barbiturate intoxication, dehydration, hepatitis, infection (esp. Gram negative), diuretics (Esp. NH_4Cl and thiazides), narcotics, diarrhoea and paracentesis.

Coma is usually preceded by personality changes (behaviour, judgment, affect), agitation, confusion, muscular rigidity and tremulousness. Examination may reveal signs of liver disease as well as the characteristic—but not pathognomonic—flapping tremor.

Lab—Bloor NH_3 is not usually available. Liver function tests are abnormal and there are specific EEG patterns. The diagnosis is largely clinical.

5) Respiratory

CO_2 narcosis—usually seen in emphysematous patients and is preceded by mental confusion, hallucinations, delirium and severe headache.

Respirations are decreased and cyanosis is present. Laboratory work reveals increased pCO_2 with decreased pO_2 and pH.

CO poisoning—there may be a history of headache and confusion. The mucous membranes (esp. lips) are characteristically "cherry" pink. Diagnosis is made by a special test for carboxyhemoglobin.

6) Endocrine

Addisonian crisis—is due to primary disease, or suppression by exogenous steroid, symptoms appearing after the patient is subjected to stress (eg. operation, infection) Diagnosis: hypotension, Na^+ less than 120 mEq/L with elevated K^+, decreased glucose.

Myxedema coma—rare; seen in old women, usually during the winter.

C) Infection

Meningococcus—The Waterhouse-Friderichsen syndrome consists of septicemia (usually meningococcus), massive skin hemorrhage and shock. It is commoner in children under five. The diagnosis is easily made in patients with fever, skin lesions and meningitis—but meningitis is *not* a usual feature.

D) Circulatory Collapse

—Infarct, coronary disease, arrhythmias, pulmonary embolus. Diagnosis: hypotension, ECG, SGOT.

E) Post-Ictal

The coma is usually brief (less than ½ hour) and a history of epilepsy is obtainable. The convulsion is often due to cessation of medication or excess alcohol intake. Check clothing for pills, Dr.s name, incontinence.

Examination may reveal scars on tongue or buccal mucosa, bruises and occasionally gingival hypertrophy from prolonged Dilarhn intake. Plantar responses may be extensor for a short time after a major convulsion.

F) Hypertensive encephalopathy

This rare condition is characterized by headache, convulsions and papilledema in the presence of extremely high blood pressure.

G) Thermic—heat stroke, lightening, exposure.

H) Hysteria

The patient in hysterical 'coma' appears unconcious but usually shows some response to external stimuli. An attempt to elicit the corneal reflex often results in vigorous contraction of the orbicularis oculi. Rigidity may be present and increase in proportion to the examiner's efforts to overcome it. Signs of organic disease are absent.

2. *No Focal Signs CSF changes present*

A) Meningitis

The onset is characterized by fever, headache and neck pain or stiffness. The examination discloses nuchal rigidity, Kernig's sign (with hip and knee fully flexed, unable to extend knee) and Brudzinski's sign (flexion of neck causes flexion of lower extremities).

The suspicion of intracranial infection is strengthened if there's a source of infection. eg. sinusitis, mastoiditis, otitis media, alveolar abcess, SBE, pulmonary abcess, bronchiectasis. After checking the fundi, an L.P. should be done. Gram stain and culture may reveal the organism.

B) Subarachnoid Hemorrhage

Is usually due to a Berry aneurysm, occasionally to trauma, tumour or A-V malformation. If massive, it can result in coma.

It occurs between the ages of twenty and fifty, and is accompanied by severe headache and vomiting. Examination reveals nuchal rigidity, +ve Kernig's sign and occasionally hypertension. Subhyaloid hemorrhages may be visible in the optic fundi. Oculomotor paralysis of one eye is often associated with an aneurysm of the anterior portion of the circle of Willis. The CSF is bloody and under increased pressure.

3. *Focal Signs with/without CSF changes*

A) Head Injury

Any head injury may result in intracerebral, subdural or extradural hematoma, presenting in coma either as a direct result of the part of the brain involved or because of secondary brain stem compression. A

history of trauma is obtainable in only 50% of subdural hematomas. The history is most likely to be negative in the elderly, in alcoholics and in patients or anti-coagulant therapy.

Signs of trauma include visible hematomata, CSF rhinorrhea and otorrhea and skull fractures.

If the intracranial lesion is rapidly expanding, the patients condition quickly deteriorates, with the development of papilledema and a fixed, dilated pupil on the side of the lesion. The pupillary change is due compression of the oculomotor nerve, by a herniated hippocampol uncus.

For a guide to investigation and treatment of head injury, see reference 19.

B) Primary intracerebral hemorrhage

The patients is usually over 40 with a history of hypertension. The coma is rapid in onset and preceded by headache.

Examination reveals a stiff neck, focal signs and occasionally, papilledema The CSF is bloody and under increased pressure. If the hemorrhage is progressive, the pupils will continue to dilate (1st on the side of the lesion) until fixed and non-reactive.

C) Infarct

Embolism — embolism of a large vessel has an abrupt onset and occurs in the patient with a source of emboli. Examination reveals paralysis, and occasionally, the results of embolization to the conjunctiva and retina. The CSF is usually normal.

Thrombosis—occurs in the elderly, is slower in onset and there is often a history of previous attacks due to cerebro-vascular insufficiency. Coma results only if infarction is extensive or involves the brain stem. Paralysis is demonstrable if coma is not too deep. CSF is usually normal.

D) Space-occupying Lesion—tumour, abcess

The onset is gradual (a rare exception is hemorrhage into a tumour) with signs of increased intracranial pressure. Coma is a late manifestation and is usually preceded by personality changes or focal signs. A chest film should always be taken.

On examination focal signs are demonstrable and papilledema may be present. The CSF pressure and protein are both often elevated.

Although ninety-five percent of patients presenting in coma will fall into one of the above-mentioned groups, remember that the evidence may be misleading, eg. a diabetic may have a stroke, head injury may be a result of alcoholic stupor or epileptic seizure, and an empty medicine bottle does not necessarily mean an overdose.

SUMMARY

The physician faced with an unconscious patient must keep the patient alive and prevent disabling damage while attempting to discover the cause of the coma. The emergency management is concerned with the maintenance of an adequate airway, the correction of shock when present and the treatment of cerebral edema. Diagnosis is made by history (witnesses, relatives, etc.), physical examination and lab tests. A differential diagnosis of the most common causes has been discussed. The possibility of dual pathology should always be considered. Although coma is often a discouraging prognostic sign, it is frequently reversible, and its depth is not always an indication of the severity of the basic disorder.

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Headache

M. J. Soboloff 6T6

INTRODUCTION

Headache is one of the commonest symptoms with which the physician is presented, either as the chief complaint, or as a troublesome problem mentioned in the functional enquiry. Vascular, tension, and psychogenic headaches, as well as combinations of these, comprise 90% of the headaches presented to the general practitioner. The remaining 10% constitute an important minority group. It is the purpose of this article to present some of the features distinguishing the common minor headaches from the uncommon, but more serious headaches.

CLASSIFICATION[11]

1. Vascular headaches
   —migraine
   —migraine variants
2. Psychogenic headaches
   —conversion
   —tension
3. Headache associated with intracranial disturbance
   —arteriosclerotic brain disease
   —vascular anomalies
   —aneurysms
   —tumours
   —infections
4. Headache associated with extracranial disease
   —eye
   —ear
   —nose and sinuses
   —bones of skull and neck
5. Headache associated with cranial trauma
6. Headache associated with systemic disease
   —allergy
   —arteritis (temporal)
   —fevers
   —infection
   —hyperthyroidism
   —hypertension

INVESTIGATION

A complete history must be taken, followed by a thorough physical examination. The importance of a complete examination may be illustrated by this example; it is not difficult to attribute a chronic cough to smoking, overlooking the possibility of chronic chest disease or carcinoma, thus missing the diagnosis of metastatic disease, or a curable brain abscess.

History

1. *Onset*
   —When did it begin?
   —Was this the first attack?

If the patient is unable to say exactly when it began, this may be significant, as it suggests an insidious onset, e.g. an enlarging intracranial mass.

2. *Mode of onset, Duration and Progression*
   —How did it begin?
   —Has there been any change?

A headache, slowly increasing in severity and in frequency of attacks, is suggestive of an expanding lesion, e.g. a subdural hematoma or a tumour, whereas the vascular headaches characteristically have an abrupt onset.

3. *Periodicity*
   —When does it occur?

An occipital headache, worse in the morning, and improving as the day goes on, suggests malignant hypertension. On the other hand, a headache which is worse after a heavy day of paper work is probably due to eyestrain. Still another example, is the sinus headache (surprisingly a rare cause of headache), which begins about one hour after arising, and is usually gone by 3 to 4 P.M.

Headache which awakens the patient from sleep is ominous, suggesting intracranial disease or hypertension, whereas that which is relieved by sleep is more likely of a less serious etiology.

4. *Precipitating Events*
   —What brings it on?

A headache brought on by coughing, bending, lying down or straining, i.e. an exertional headache, suggests an intracranial mass (often posterior fossa), e.g. an acoustic neuroma. However, these activities may also increase a less ominous headache which is already present e.g. tension or sinus headache. Also, an exertional headache may be present with no demonstrable organic disease.[9]

Inquire about alcohol or drug intake (e.g. nitroglycerin), as these may be directly responsible for the headache.

5. *Warning*
   —Does he feel the headache coming on?

During the aura of a migraine attack, the patient may experience various sensory or motor disturbances.

6. *Quality*
   —How severe is it?
   —What type is it?

Avoid asking leading questions. The psychogenic headache is most often described as a "tight band", and occasionally as a "nail" or "heavy weight". It is often described in dramatic terms. The migraine headache is usually described as throbbing, and occasionally the patient feels it coinciding with the heart beat. A bursting headache may be psychogenic, but keep in mind the possibility of increased intracranial pressure.

A question that is often of value is: What recent change, if any, has made the patient see a doctor now?

7. *Location and Radiation*
   —Where is the pain?
   —Is it localized?

Pain from deeper structures is not as well localized by the patient as is superficial pain. For example, the pain of temporal arteritis can be accurately localized, whereas that of an intracranial mass is often vague.

Classical migraine is unilateral, but involves the opposite side in different attacks. A headache which always involves the same side, should alert one to the possibility of aneurysm or tumour.

Pain radiating to the shoulders or neck may be a symptom of cervical spondylosis.

8. *Relief*
   —What relieves it?

Headaches relieved by sleep are usually psychogenic, or due to eyestrain whereas if relief is obtained by sitting up; this suggests raised intracranial pressure.

Vascular headaches, such as migraine, are more apt to disappear spontaneously. Relief by aspirin is not usually a reliable sign.

9. *Any Preceding Event*
   —Is there a history of injury, recent or distant?
   —e.g. a chronic subdural hematoma can cause symptoms for months.
   —Is an infection present, superficial (e.g. a boil), or (e.g. lung), providing a primary focus for a brain abscess?
   —Has there been a recent emotional upset, providing the basis for a tension headache?

10. *Family History*
   —Is there a family history of migraine?

Do not be led astray by a positive family history, as this may be coincidental.

11. *Associated Symptoms*

This may be the most significant part of the history. Is there any local tenderness? — e.g. as in temporal arteritis or osteomyelitis.

Is there nausea and vomiting? — This may be a symptom of increased intracranial pressure, migraine or intoxication.

Is there any nasal stuffiness or discharge? — This may be present in sinusitis, and in cluster headaches.

Is there any visual disturbance? — This is common in migraine attacks, but may also be a sign of incipient thrombosis, — e.g. in carotid artery insufficiency, there may be episodic blindness in the ipsilateral eye, associated with headache.

Is there dizziness or ataxia? — These symptoms are strongly suggestive of intracranial disease.

PHYSICAL EXAMINATION

Although most headaches can be diagnosed from the history alone, a careful physical and neurological examination must be done, followed by appropriate laboratory work and special tests where indicated. Study especially the cranial and paracranial structures; the scalp for local tenderness; the sinuses and ears for infection; the eyes for iritis, glaucoma, retrobulbar neuritis and papilledema; look for localizing neurological signs, such as the third nerve palsy that may be associated with a ruptured berry aneurysm; the neck for stiffness and signs of cervical spine disease.

LABORATORY

Blood

The investigation should include routine blood work, such as Hgb, W.B.C., and E.S.R. This is occasionally of assistance, e.g. — elevated E.S.R. in temporal arteritis.

Cerebrospinal Fluid

If the history and physical examination suggest intracranial disease, such as meningitis, aneurysm or tumour, a lumbar puncture is indicated. A smear and culture should be done if infection is suspected.

SPECIAL TESTS

X-Ray

It may be necessary, for the purpose of diagnosis and/or localization, to resort to specialized x-ray techniques, such as arteriography or encephalography. These tests are not without danger, and are reserved for those cases which clearly may benefit from them; e.g. a suspected enlarging intracranial hematoma.

OTHER TESTS

Echo Encephalography

This is a simple test, based on the principle that a unilateral cerebral lesion will push the mid-line structures within the cranium toward the opposite side. It is

often valuable in confirming the diagnosis of a hematoma, and is a simple, safe procedure.

E.E.G. AND BRAIN SCAN

These tests require specialized interpretation.

CONCLUSION

Keeping in mind that most headaches are benign, the following danger signals should alert the investigator to the possibility of serious disease:[7]

1. Headache of sudden onset.
2. Headache of long duration with a sudden change in pattern or severity.
3. Headache brought on by coughing or bending.
4. Headache awakening the patient from sleep.
5. Headache associated with other symptoms or signs, as previously described.

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DIFFERENTIATION OF VARIOUS TYPES OF HEADACHES

	Migraine	Migraine Variants e.g. Cluster	Intracranial Lesion	Tension*
Onset Stage of Life	Any	Often after 35	Any	Any Usually after 20
Rate of Onset	variable	abrupt	gradual	variable
Time of day	Usually morning	often during sleep	variable often in morning	Usually end of day
Prodrome	Present usually	infrequent	infrequent	infrequent
Precipitating Events	Maybe emotional event		–Maybe trauma if a hematoma –Exertional	Maybe emotional event
Nature	Pulsating	Boring	Dull usually	Dull or sharp
Duration	Minutes to days	under one hour	Gradually becomes more prolonged	No pattern
Site	Anywhere Usually one temple	–Eye, Neck and Face –unilateral	–variable –often vague	Usually frontal or occipital
Relief	Spontaneously	Spontaneously	Often by sitting up	Often by sleep
Associated Symptoms	May be any of a number of abnormal sensations	May be photophobia and nasal stuffiness	May be nausea and vomiting, dizzyness	Variable
Physical Abnormalities	Maybe during aura		May be localizing neurological signs	Usually none

*Tension headache may be emotional (secondary to anxieties, stresses etc.), or structural (secondary to structural tissue changes, e.g. cervical spondylosis, spinal injuries, etc.). The distinction is often difficult.

The usual emotional headache is described above. If the following signs are present, consider the possibility of structural headache.

1. Unilateral pain
2. Response to aspirin or physiotherapy
3. Modification by position and activity
4. If desired in simple, concise terms
5. If there are periods of relief
6. If it sounds "progressive"

William T. Morton

In the year 1844 a young dentist named William Morton made a startling discovery which was to revolutionize the practice of dentistry and surgery. He described it this way:

"I studied in the office of Dr. Charles T. Jackson, of Boston, and in order to employ my time to the utmost advantage, I resided in his family. One day, in casual conversation upon my profession of dentistry, I spoke of the operation of destroying the nerve of a tooth. . . . Dr. Jackson said, in a humorous manner, that I must try some of his tooth-ache drops. . . . Dr. Jackson then added, that as this ether might be applied with advantage to sensitive teeth, he would send me some. The conversation then turned upon the effect of ether upon the system, and he told me how the students at Cambridge used to inhale sulphuric ether from their handkerchiefs, and that it intoxicated them, making them reel and stagger.

The successful application I had made of the ether in destroying the sensibility of a tooth, together with what Dr. Jackson told me of its effects when inhaled by the students at college, awakened my attention, and having free access to Dr. Jackson's books, I began to read on the subject of its effect upon the animal system. I became satisfied there was nothing new or particularly dangerous in the inhaling of ether, that it had long been the toy of professors and students, known as a powerful anti-spasmodic, anodyne and narcotic, capable of intoxicating and stupefying, when taken in sufficient quantity. I found that even the apparatus for inhaling it was described in some treatises, but in most cases it was inhaled from a saturated sponge or handkerchief.

In the spring of 1846. . . . I tried an experiment upon a water spaniel, inserting his head in a jar having sulphuric ether at the bottom. . . . After breathing the vapor for some time, the dog completely wilted down in my hands. I then removed the jar. In about three minutes he aroused, yelled loudly, and sprung some ten feet, into a pond of water . . . early in August; and it being hot weather, and I being somewhat out of health, I went into the country, and abandoned the experiments until the middle of September. With the autumn and the restoration of health, my ambition led me to resume my experiments.

I . . . waited impatiently for some one upon whom I could make a fuller trial. Toward evening a man (Eben Frost), residing in Boston, whose certificate is in the appendix, came in, suffering great pain and wishing to have a tooth extracted. He was afraid of the operation and asked if he could be mesmerized. I told him I had something better, and saturated my handerchief, gave it to him to inhale. He became unconscious almost immediately. It was dark, and Dr. Hayden held the lamp, while I extracted a firmly rooted bicuspid tooth. There was not much alteration in the pulse, and no relaxation of the muscles. He recovered in a minute, and knew nothing of what had been done to him. . . . This was on the 30th of Sept., 1946. This I consider to be the first demonstration of this new fact in science."

William Thomas Green Morton was born in Charlton, Massachusetts, the son of a farmer. After a public and high school education he worked as a clerk and salesman. Being somewhat bored with this, he began studying dentistry at the Baltimore School of Dental Surgery. He was at that time twenty-one years of age. Following graduation he began a thriving practice in partnership with Horace Wells.

In March 1844, Morton enrolled at Harvard Medical School, meanwhile continuing his dental practice. He completed two terms of Harvard but did not receive his medical degree. It was while studying medicine that he lived with Dr. Charles Jackson, whose success with ether drops used as a local anaesthetic during the filling of teeth was familiar to Morton.

Meanwhile, Morton was searching for a nontoxic agent to produce insensibility to pain during extraction of teeth, and for general surgical purposes. He knew that Dr. Wells used nitrous oxide for dental extraction, and he knew of "ether frolics". As well, he was aware that experimental inhalation of ether would produce temporary insensibility.

Two requirements remained to be satisfied to justify the inhalation of ether for physical insensibility during a surgical operation: a device for efficient administration of ether as well as surgical team and a patient.

The conditions were fulfilled on October 16, 1846. An ether cone was made for Morton, the patient was Gilbert Abbott, and the surgeon was John Collins Warren, Hersey, professor of anatomy and surgery at Harvard and senior surgeon at the Massachusetts General Hospital. The surgeon removed a tumor from the patient's neck after successful induction with ether.

The event was casually mentioned in the *Boston Medical and Surgical Journal*, October 21, 1846, as follows:

"Strange stories are related in the papers of a wonderful preparation in this city, by administering which a patient is affected just long enough, and just powerfully enough to undergo a surgical operation without pain."

A more complete report followed later.

"On the 16th of October, 1846, an operation was performed at the hospital, upon a patient who had in-

haled a preparation administered by Dr. Morton, a dentist of this city, with the alleged intention of producing insensibility to pain. Dr. Morton was understood to have extracted teeth under similar circumstances, without the knowledge of the patient. The present operation was performed by Dr. Warren and though comparatively slight, involved an incision near the lower jaw of some inches in extent. During the operation the patient muttered as in a semi-conscious state, and afterwards stated that the pain was considerable, though mitigated; in his own words, as though the skin had been scratched with a hoe. There was, probably, in this instance, some defect in the process of inhalation, for on the following day the vapor was administered to another patient with complete success. A fatty tumor of considerable size was removed by Dr. Hayward, from the arm of a woman, near the deltoid muscle. The operation lasted four or five minutes, during which time the patient betrayed occasional marks of uneasiness; but upon subsequently regaining her consciousness, professed not only to have felt no pain, but to have been insensible to surrounding objects, to have known nothing of the operation, being only uneasy about a child left at home. No doubt I think, existed in the minds of those who saw this operation, that the unconsciousness was real; nor could the imagination be accused of any share in the production of these remarkable phenonema."

At first, Morton withheld the chemical nature of the substance calling it "Letheon". The true nature of the compound was later disclosed and a patent was granted on October 28, 1848. Upon advice of others, Jackson's name was included as a patentee. This failed to satisfy Jackson who created such a local and national furor, that glory was outweighed by extreme bitterness.

Morton's great days as a scientist were over. The remainder of his time was devoted to the establishment of priority for the ether discovery. In addition to whatever personal satisfaction Morton received from his great contribution, he was awarded an honorary M.D. from the University of Baltimore and $1,000 from Massachusetts General Hospital. An award of 5,000 francs was offered by the French Academy of Medicine but was refused by Morton since it was made jointly to Morton and Jackson.

The last bitter years of Morton's life were spent in agricultural pursuits. He died in extreme mental anguish in Central Park, New York in 1868. Jackson died in an insane asylum after being committed in 1873, and Wells took his own life in 1848.

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Abstract

Attitudes towards "Scientific" Medicine around 1700

Lester S. King, M.D.: Bull. of the His. of Med., Vol. 39, No. 2, March April 1965, pp. 124 - 133.

The late seventeenth century was an era of particularly intense conflict between the old and the new in scientific values. Opposing new doctrines, in the tradition of Aristotle and Galen, stood the old science. In contrast, stood the new scientific, which, according to Francis Bacon, offered power over nature, and joy, intrinsic in the acquisition of knowledge, as wrote Robert Boyle.

In 1668, a young clergyman, Joseph Glanvill Published an analysis attacking the old and defending the new. He praised Harvey's discovery of the circulation and extolled the virtues of blood transfusion to benefit "pleurisies, cancers, leprosies, madness, ulcers, smallpox, dotage, and all such like distempers." Shadwell's Restoration comedy, *The Virtuoso,* represents the cultural resistance to the scientific advance. The virtuoso disdains "practick" and concerns himself, in a series of humorous episodes, only with the speculative and inapplicable. Sir William Temple, in an essay, makes the point that the new knowledge had contributed little of practical value to society at that time. Jonathan Swift's famous description of Gulliver's voyage to Laputa savagely satirizes the Royal Society.

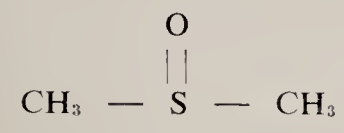
In medicine, the writings of Giorgio Baglivi best characterize the dichotomy between the old aphoristic method and the hypothetical-deductive system of the new science. He made a sharp distinction between the theory and practice of medicine. As the guide to treatment, Baglivi favoured the aphorism—the distilled experience of the physician, a broad generalization derived from observation of many specific cases without any attempt at explanation. Whereas he indicated that as far as theory was concerned, the moderns had made advances over Galenists, their practice of medicine was, in fact, inferior.

Despite the insistence of Bacon that knowledge is power, in medicine, at least, the practical application of science in the late seventeenth century lagged behind theoretical advance. Through the eighteenth century a discerning empiricism, in contrast to Baglivi's simple minded observation, coupled to soaring flights of speculation produced great scientific progress.

M.S.

Recent Advances

Dimethyl Sulfoxide . . . DMSO



"In the lay press, the therapeutic promises of dimethyl sulfoxide have merited the sobriquet 'miracle drug.' This attribution is not altogether assignable to journalistic licentiousness if the substance can be shown to possess but a modicum of the pharmacological virtuosity claimed it."

A. M. Kligman — JAMA Sept. 6, 1965

Many, if not most, medical practitioners might at the present time take exception to the discussion of DMSO as a "recent advance" despite the fact that this agent has been hailed with varying degrees of euphoria from such august sources as Time, Newsweek, Life, Saturday Evening Post, Confidential and Pageant.[5] In fact, DMSO is a highly polar(stable, hygroscopic, organic liquid with exceptional solvent and penetrant properties, miscible with water, lipoids and organic solvents. A byproduct of the pulp and paper industry, it was first isolated in 1867 and has since found numerous scientific and industrial uses (e.g. a solvent for resins, fungicides, dyes and pigments; a catalytic reaction medium; an extractant; and a preservative for living cells and tissues during freezing).[2] For several years, its possible medical uses were quietly investigated on a small scale by a group of workers at the University of Oregon. In December 1963 an agreement was signed between Crown Zellerbach Corporation (the producer) and the University Medical Faculty making arrangements for future patenting and clinical investigation. Shortly thereafter, publicity releases from the University were made directly to the news media, generating a public enthusiasm which is yet to be shared by the better informed scientific community. The usual hesitancy of the medical profession in accepting new "wonder drugs" has undoubtedly been enhanced in this case by a distaste at the sensationalism surrounding the initial announcement. Despite the earlier irregularities, DMSO is receiving a thorough trial and we are now in a position to assess some of the findings pro and con.

The original paper[4,6] published by Jacob and his coworkers at Oregon, ascribed the following pharmacologic actions to DMSO:

1) a penetrant carrier
2) a local analgesic agent
3) anti inflammatory adjunct
4) bacteriostatic agent
5) diuretic
6) tranquilizer
7) potentiator of other compounds

Clinical interest has centred largely on the possible effect on musculoskeletal inflammation and on the use as a vehicle for agents whose effectiveness would be enhanced by more rapid or more complete absorption. The substance has been found to have an exceptionally low toxicity by all routes of administration but most clinical trials have dealt with topical applications of a 60 to 90% solution with a cotton tipped applicator. A quantity of 6 to 8 ml. is applied over a knee, 8 to 15 ml. over a shoulder.[4] Most patients have reported a garlic like odour appearing on the breath after several applications; apparently due to a breakdown product, dimethyl sulfide. The patients soon adapt to this garlic odour but it has made it difficult to conduct double blind studies on the drug.

The Oregon group has recently published a large clinical trial showing the following impressive results:[1]

acute musculoskeletal injuries	195	of 210	improved
acute subacromial bursitis	22	of 25	improved
chronic subacromial bursitis	32	of 40	improved
osteoarthritis	88	of 110	improved
rheumatoid arthritis			
(grades 1, 2)	60	of 80	improved
(grades 3, 4)	30	of 70	improved
gouty arthritis	3	of 5	improved
Scleroderma	4	of 5	improved
Dupuytren's contracture	3	of 3	improved

This group has also studied the action of DMSO in cases of intractable pain where all conventional treatments has failed:[4]

phantom pain	8	of 11	relieved
tic douloureux	9	of 11	relieved
post traumatic pain	10	of 10	relieved
postoperative pain	5	of 5	relieved

(following drainage of an empyema, an abdominoperineal resection, resection of a benign oesophageal tumour, resection of a benign spinal cord tumour, and a herniorraphy)

These postulations and results would be somewhat more acceptable and exciting if a methodologically sound investigation had been conducted and theories as to mechanism of action set forth (in the cases of pain relief, time of onset of action varied from 3 minutes to 13 days . . . no explanation offered.)

Physicians of the Cleveland Clinic have reported considerable improvement in the cutaneous manifestations of systemic scleroderma, especially in healing ischemic ulcers of the finger tips.[2]

A comprehensive, impartial evaluation of DMSO has recently come from A. M. Kligman, Professor of Der-

matology at the University of Pennsylvania.[2 3] After an extensive study of pharmacologic properties he arrived at a number of conclusions which seem to have clinical relevance:

1) DMSO enters the skin with great speed, permeates the stratum corneum and somehow creates pathways for the diffusion of a great variety of polar and non polar substances. This penetrant action does not involve any destruction of the horny layer. Experimentally, DMSO has been shown to increase uptake of antiperspirants, topical steroids and various dyes.

2) DMSO was shown to cause histamine release resulting in wheal and flare formation and degranulation of mast cells. There was some drop in observed in the number of circulating basophils with prolonged administration. There is a potent vasodilator action and a tendency to pool blood in the peripheral circulation. Amplification of circulation is suggested as a possible explanation for therapeutic value in traumatic injuries accompanied by edema.

3) It has a mild antibacterial action but this is unremarkable by modern standards and is far inferior to alcohol. Concentrated solutions frequently applied were able to reduce the resident microflora in the axilla by 95%.

4) DMSO is a mild antifungal agent proven moderately effective against tinea pedis. It may prove most effective in treatment of ringworm where the fungus is confined to the horny layer. In this instance DMSO could serve as a vehicle for a potent fungicide.

Kligman was unable to demonstrate a local anaesthetic or tranquilizing effect, and saw no therapeutic value for DMSO in the treatment of thermal burns, contact dermatitis or ultraviolet burns. He confirmed the low systemic toxicity of the drug and found that the skin rapidly became tolerant to the mild irritation of continuous exposure.

It should be pointed out that DMSO is still under investigation by the Food and Drug Administration of the United States Government and is unlikely to be available for general use in North America in the immediate future. For the most part, the extravagant claims made, seem premature and unsupported, and judgment should therefore be reserved until the results of further careful studies are available.

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Abstract

Some Less Common Neurological Findings in Leprosy

—S. G. BROWNE

Journal of the Neurological Sciences, Vol 2, No. 3, May/June 1965.

The common neurological findings in leprosy of enlarged, hard, *tender*, sometimes painful nerve trunks, at subcutaneous sites where the nerves pass over bones or joints and thus are more susceptable to trauma are mentioned.

From the personal observation of about 20,000 cases, the author describes signs, less commonly found in the existing literature. The importance of localized parasthesias and neuralgias antedating cutaneous symptoms is emphasized. Presentation in less commonly affected peripheral nerves, enlargement of cutaneous nerve twigs, delayed pain, polyneuritis without skin pigment changes, sensory and motor impairment, and occasional eventual symmetry of lesions are described. Neuropathic disturbances of vasomotor and sweating functions, pigmentation, hair growth, and "trophic" ulcers are noted. The pathophysiology of the above findings is discussed.

The predeliction of M. Leprae for peripheral nerve tissue is considered with relation to the neuropathies of experimental mycobacteria infection, collagen and experimental autoimmune diseases, and the *Guillain-Barré* syndrome. The possible effects of antibody response, temperature, trauma, and edema of the nerve trunk on the sites and nature of the presenting signs are reviewed.

K.P.H.P.

Abstracts

Some Observations on the Natural History of Intracranial Aneurysms

G. H. du Boulay, F. F. R.: The British Jour. of Rad., Vol. 38, No. 454, October 1965, pp. 721 - 757.

In a series of 1,345 patients on whom cephalic angiography was performed, 197 had intracranial aneurysms. The histories, radiographs and, where relevant, the operation notes and pathological findings were examined. In addition, a histological study of the cephalic arteries of 160 species of mammals and birds was undertaken.

It was found that all the aneurysms showed atherosclerotic change and that the distributions of aneurysms and atherosclerotic lesions in the cerebral circulation were similar. Whereas, it is admitted that a single basic lesion may predispose to both aneurysm and atheroma the author presents grounds for rejecting the primary importance of discontinuity in the medial muscle coat of the intracranial arteries in the etiology of aneurysms. The hypothesis is made that the gap in the musculature, filled with elastic tissue, which is normally seen at the site of arterial branching, is to prevent stretch deformity and stenosis at this site when the muscle contracts.

The sex incidence of aneurysms is considered. Past the age of 35 years this study finds a preponderance of the disease among women. Aneurysm in the female has a worse prognosis than the male.

Because microscopic aneurysms are so rarely seen the author concludes that the initial formation of aneurysms is rapid. Furthermore there are often sudden (frequently asymptomatic) changes in the apparent radiographic size of existing aneurysms. Illustrative examples are cited. A locule may suddenly appear on an existing aneurysm. Although hemorrhage is not necessarily accompanied by loculation, loculation when it occurs is nearly always associated with bleeding.

Large aneurysms behave differently from the smaller ones just discussed. Surrounded by dense organized clot and fibrous tissue, they have probably grown slowly. Subarachnoid hemorrhage in these aneurysms is not very common but does occur.

The growth of aneurysms and the occurrence of subarachnoid hemorrhage is a balance between such factors as atheromatous change and blood pressure, and fibrosis and organization of clots. Small leaks causing only transient headache are common and may precede a major hemorrhage.

Radiographic localization of a site of hemorrhage is complicated by the accompanying widespread arterial spasm. A multilocular aneurysm among several simple ones is probably the site of hemorrhage. Ventriculographic location of a hematoma is the most reliable indicator of the bleeding site. Bilateral carotid arteriograms are recommended.

The author estimates that the incidence of silent aneurysms is about 4.5 per 1,000 with the majority occurring in the older age groups. Since the death rate from subarachnoid hemorrhage is only 0.24 per 1,000 in spite of the very high mortality of frank subarachnoid hemorrhage, the course of the disease of intracranial aneurysm is not as bad as has generally been supposed. M.S.

Cancer of the Bladder, Biochemical Factors in its Etiology

W. K. Kerr, M.D., F.R.C.S.(C), Martin Barkin, M.A., M.D., B.Sc.(Med.) and Z. Menczyk, A.R.T.: Can. J. of Surg., Vol. 7, No. 4, October 1964, pp. 414 - 419.

For a number of reasons, research into the etiology of bladder cancer has concentrated on biochemical aspects of the disease. As early as 1895, Rehn had noted that 3 workers of a dye-works employing 45, had a bladder tumour. This tumour was termed "aniline workers' cancer". Workers have investigated the geographical incidence of bladder tumours and implicated such factors as endemic bilharzial infestation.

In the search for a common biochemical explanation, aniline and related aromatics such as 2-naphthylamine were found to be responsible. Oral administration to dogs of 2-naphthylamine over periods of up to two years produced vesical cancer in 80% of dogs so treated. Other investigators showed that diversion of the upper urinary tract into the sigmoid colon spared the bladder. Further studies established that the carcinogenic aromatic amines had to be metabolized to their ortho-aminophenol derivatives, then excreted into the urine, where, by direct contact with the urothelium, carcinogenesis was stimulated.

High levels of beta-glucuronidase occur in the urine of patients with bladder cancer. The importance of beta- glucuronidase in the liberation of free ortho-aminopheniols from the excreted, inactive, conjugated forms remains in doubt.

The metabolism of tryptophan was found to be an endogenous source of ortho-aminophenols. Implantation experiments showed that certain tryptophan metabolites were carcinogenic. These compounds, in particular, 3-hydroxyanthranilic acid, have been found in excessive amounts in patients with bladder cancer.

Whereas the liver is the major site of tryptophan metabolism, there is evidence that the urinary tract and the urinary tract containing tumour are sources of ortho-aminophenal precursors derived from tryptophan.

Investigators report that the abnormal metabolism that produces these precursors may be corrected by large doses of pyridoxine (vitamin B6).

To prove conclusively that tryptophan has a role in carcinogenesis, it must be shown that derangement in metabolism precedes the development of cancer and is not secondary to cancerous change. At least it must be shown that deranged metabolism continues after removal of a bladder tumour. Toward these goals, research continues. M.L.S.

Abstract

Dumping Syndrome after Gastric Surgery

T. Wiznitzer et al.: Archives of Surgery, Vol. 91, No. 3, Sept. 65, pp. 419 - 423.

A comparative study was made of clinical and experimentally induced dumping syndrome in 25 patients after gastroenterostomy with vagotomy and in 25 patients after pyloroplasty with vagotomy. Eight intact people with no gastric disease were included as controls.

Clinically, the incidence and severity of the dumping syndrome as found to be greater in the patients with pyloroplasty. Oral administration of 150 cc. of 50% glucose produced dumping symptoms and signs (dizziness, vomiting, cramping abdominal pain, diarrhea, hypotension and tachycardia) of varying severity in both postoperative groups. There was no significant difference in the incidence and intensity of experimental dumping in the two groups.

Plasma volume was measured in all subjects. In the individual case, there was generally good correlation between the drop in plasma volume after ingestion of the test meal and the severity of symptoms, but the fall in volume required to produce symptoms, varied from patient to patient. No volume change and no dumping symptoms were observed in the controls.

A brief discussion of the present study and various factors in the production of the syndrome follows.

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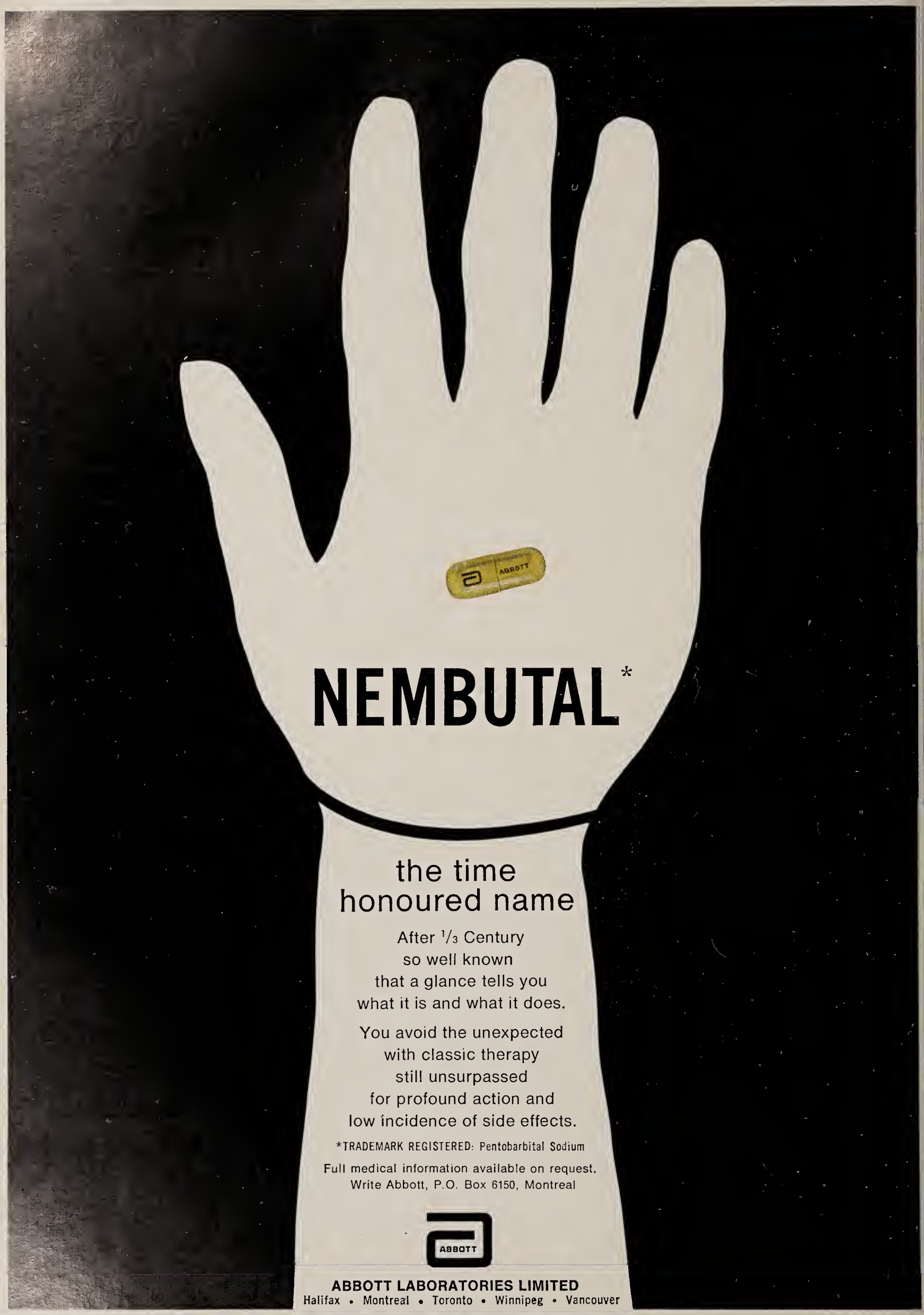

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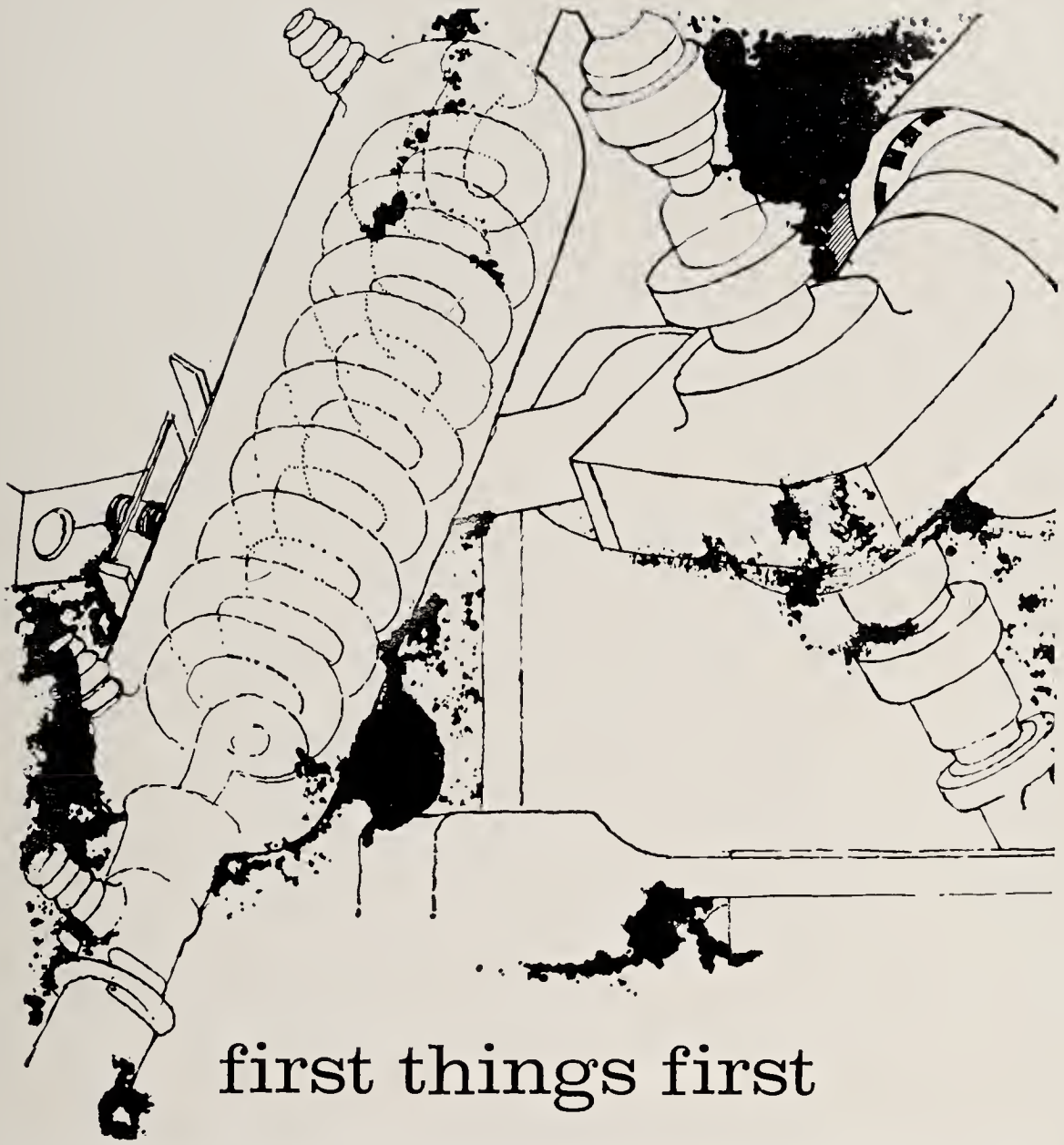

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